Congenital Heart Disease in Pediatric and Adult Patients

Anesthetic and Perioperative Management

Ali Dabbagh
Antonio Hernandez Conte
Lorraine N. Lubin
Editors

Second Edition

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To our colleague and friend

Dr. David Atkinson

We celebrate his wit, his devotion to pediatric cardiology, and his courage in the face of his personal journey with congenital heart disease.

To the healthcare providers who perished caring for patients due to the Covid-19 Pandemic, we will not forget your sacrifice.

To our families, it would be impossible to achieve this goal without their unwavering support.

Foreword

The second edition of *Congenital Heart Disease in Pediatric and Adult Patients* provides an updated, in-depth appreciation of the current therapies and modalities available for the management of two similar and overlapping complex clinical populations.

For the students of history in medicine, it will not come as a surprise that the modalities and management of congenital heart disease have experienced a truly remarkable trajectory since the first ligation of patent ductus arteriosus in 1938.

Drs. Dabbagh, Hernandez Conte, and Lubin have created a comprehensive reference textbook that contains contributions from a variety of internationally recognized experts in the disciplines of anesthesiology, cardiology, cardiac surgery, and critical care. The diversity of authors and detailed topics covered highlight the importance of the interdisciplinary management that is necessary to manage patients in this complex and expanding clinical arena. The second edition continues in combining comprehensive literature review with practical knowledge that can be utilized by clinicians in everyday practice.

Today's clinicians and scientists now have the tools, techniques, and therapies to truly revolutionize the care of patients with congenital heart disease. Today, we have the privilege of caring for patients with a variety of treatment options that were not imaginable when the visionary pioneers of this field set forth this new discipline. The information provided in the second edition ensures that all who are entrusted with the care of patients with congenital heart disease are armed with the most contemporary and evidence-based knowledge and tools.

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Roberta L. Hines

Preface

Congenital heart disease (CHD) continues to be the most prevalent birth defect and leading cause of congenital anomaly-related infant mortality. In the United States, more than 40,000 infants are born yearly with CHD, and 0.8%–1.2% of infants worldwide are consistently affected with CHD. Despite advances in detection and treatment, the global incidence remains stable with only 15% of cases being attributable to a known cause. With improved diagnostic and imaging techniques, surgical innovation, interventional cardiology procedures, anesthetic care and critical care management, the lifespan of the patient with CHD is approaching the lifespan of the unaffected population. The ratio of pediatric to adult patients has now switched to approximately 30% pediatric patients to 70% adult patient population. The ratio of pediatric and adult patients in the 1970s was reversed and reflects the shift in epidemiology of CHD. More than 90% of patients with CHD are living with their CHD into adulthood, and it is apparent that this population will require knowledgeable and compassionate care from all medical specialties. While the ACHD population is continuing to grow, it has been shown that improved outcomes are seen when this unique group of patients are managed at specialized ACHD centers.

CHD is a lifelong disease with multisystemic consequences that develop due to abnormal cardiac anatomy and physiology. For this reason, it is imperative that patients with pediatric CHD are transitioned to the ACHD care team in an appropriate fashion as the patients also have the same acquired age-related comorbidities as their unaffected peers. The concept of surgical cures has passed, and lifelong palliation is the rule. Significant advances have been made with CHD and ACHD guidelines provided by experts who appreciate the unique physiology of complex lesions and the understanding that patients with moderate or complex CHD are at higher risk of long-term complications, morbidity, and mortality.

CHD represents a medical challenge that spans the life of the patient from birth and childhood through adolescence and adulthood. While patients with congenital heart disease often have significant medical challenges, they continue to want the same life milestones and experiences as their age matched peers. ***Minimizing the lifetime trauma to our patients and helping them realize their potential through optimized, coordinated care is the goal for the CHD and ACHD multidisciplinary team.*** Patients with CHD are having families and there has been a significant increase in the rate of pregnancies in the ACHD population.

While the lifespan of the patient with CHD has increased and the quality of life has become a priority, there are many patients that have complex CHD such as single ventricle palliation and other complex forms of CHD that often require cardiac transplantation. Some of the patients with severe multisystemic disease will require multiple organ transplantation including heart-kidney, heart-lung, and heart-liver transplants. The care and therapies for CHD and ACHD are constantly evolving, and our patient-centered approach is based on the unique anatomy and physiology of each patient.

The second edition of our textbook ***Congenital Heart Disease in Pediatric and Adult Patients: Anesthetic and Perioperative Management*** is a comprehensive and updated approach in the care of the congenital heart patient from birth to adulthood with a multidisciplinary approach and includes experts and specialists from the entire perioperative CHD/ACHD team. Our goal is to present to the reader our approach to the entire perioperative process, surgical decision making, anesthetic and postoperative management, and optimized, data driven management of complex problems unique to this cardiac population.

The second edition of ***Congenital Heart Disease in Pediatric and Adult Patients: Anesthetic and Perioperative Management*** is organized into six major sections. Each section describes a particular facet unique to this subspecialty and is designed to allow the clinician managing this patient population to rapidly become oriented with the specific pathologies and care issues.

Part I focuses on the history of anesthesia for CHD as well as embryology, physiology, and pharmacology. Part II entails the technical requirements for diagnostic methods and for monitoring patients undergoing medical care for CHDs. Part III focuses on the preoperative evaluation and considerations unique to patients with CHD. Part IV describes in great detail the intraoperative care of patients with CHD with specific chapters on each of the congenital anomalies. Part V expounds on the postoperative care of patients with CHDs. Part VI of the book addresses emerging trends and clinical care outside of the traditional operating room that is creating the new field of "hybrid" procedures for CHDs. Also, there are four chapters in this section discussing "Nutritional Support in Congenital Heart Disease," "Future Approaches for Anesthesia in Congenital Cardiac Surgery & Interventional Procedures," "Congenital Cardiac Surgery in Emerging Countries," and "Medical Education for Congenital Heart Disease" which deal with special aspects of CHD.

This book was written and produced during the Covid-19 pandemic, and we would like to thank all of the writers, mentors, contributors, and publishing team for their valiant efforts and expertise. As a group, we would like to thank our families and of course our amazing patients that are at the center of our efforts.

Tehran, Iran — Ali Dabbagh
Los Angeles, CA, USA — Antonio Hernandez Conte
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Contents

History of Pediatric Anesthesia and Pediatric Cardiac-Congenital Surgery

Antonio Hernandez Conte

Abstract

Pediatric surgery has a long history that dates back to the early twentieth century. In the early 1900s, pediatric medicine and surgery were undistinguishable from general adult surgical care; therefore, adult and pediatric patients were treated in a similar manner. Pediatric cardiac and congenital surgery focuses upon the surgical correction of major anomalies pertaining to the heart and surrounding vascular structures. As the subspecialty of pediatric surgery evolved in the mid-1900s, pediatric surgical care became more commonly based at children's specialty hospitals throughout Europe and the United States. In the pre-1850s, hospitals in the United States generally had no place for children outside of the maternity ward. In 1855, the Children's Hospital of Pennsylvania (CHOP) in Philadelphia opened its doors. By 1871, CHOP was performing its first pediatric surgeries, and in 1871, the first pediatric-centered medical training program was established. Pediatric surgical pioneers began to emerge as early as 1917, and a small cadre of surgeons developed the field that eventually became the norm around the United States. The birth of modern pediatric anesthesia first began in the 1930s and was closely tied to the advances being made by the respective pediatric surgeons. In the 1960s and 1970s, pediatric anesthesia entered into its first explosive period of growth fueled by translational discoveries in human biology, including fundamental understandings of the transition from fetal to postnatal circulation. The field of congenital surgery and anesthesiology was the amalgamation of multiple separate sectors coalescing into one hybridized field encompassing pediatrics, anesthesiology, cardiology, surgery, and interventional radiology.

Keywords

History of pediatric anesthesia · Development of children's hospitals · Child health
Congenital heart disease · Pediatric wellness
Pediatric surgeon pioneers

Pediatric surgery has a long history that dates back to the early twentieth century. In the early 1900s, pediatric medicine and surgery were undistinguishable from general adult surgical care; therefore, adult and pediatric patients were treated in a similar manner. Whereas in contemporary medicine, pediatric surgery is a com-

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pletely separate surgical subspecialty with different training pathways compared to a surgeon treating adult patients. It was soon discovered that the mortality rates in the younger population were extraordinarily high and that if improved results were expected, the pediatric patient would need a separate treatment approach.

Pediatric patients have traditionally been defined as patients under the age of 18; however, as will be discussed in later chapters, this age demarcation has once again become less defined as patients who manifested congenital heart disease grow into adulthood and require additional cardiologic or cardiac surgical interventions. Pediatric cardiac and congenital surgery focuses upon the surgical correction of major anomalies pertaining to the heart and surround vascular structures. As the subspecialty of pediatric surgery evolved in the mid-1900s, pediatric surgical care became more commonly based at children's specialty hospitals throughout Europe and the United States. In the period of less than 50 years, the initial development and evolution of medical and technical advances led by key scientists and physicians focusing upon care of the pediatric patient allowed the fields of pediatric surgery, pediatric cardiac/congenital surgery, and pediatric anesthesia to become a mainstay of modern-day medicine.

The Birth of Pediatrics and "Children's Hospitals" in the United States

The status of pediatric care in the 1800s and early 1900s was profoundly different than current standards in the modern era. As mentioned earlier, pediatric patients were in essence treated in a manner similar to adults. Some examples of prevailing treatments and trends included lack of understanding of intravenous therapy, and fluid balance was based on adult models. Additionally, blood transfusions were not utilized, and appendicitis was the fourth common cause of death in children. The most common surgical procedures in children were abscess drainage, appendectomies, tumors, and hernia repairs. There was 90% mortality for colostomies and intussusceptions. With the concomitant medical and surgical advances that had begun in the mid-1930s and continued thereafter in each decade, pediatric care was finally becoming entrenched in newly formed children's hospitals.

Dr. Abraham Jacobi is considered to be the father of pediatrics in the United States and offered the first lectures on pediatric disease in 1860. Generally speaking, adult medicine focused upon organ issues or technology. Dr. Jacobi believed that children warranted a broader approach with respect to child health and well-being and not just disease states. In 1880, Dr. Jacobi along with a few other physicians founded the American Medical Association's section on the diseases of children. They stressed the need for more children's hospitals and for the expansion of pediatric content in medical school curricula. By 1900, ten schools of medicine had full-time pediatricians.

In the pre-1850s, US hospitals generally had no place for children outside of the maternity ward. Childhood illnesses were, therefore, most often handled at home. When families sought medical care outside of their home, children were treated as tiny adults. This view led to high infant and children mortality rates who had been admitted to hospitals, due to improper medical care. Dr. Francis West Lewis visits the Great Ormond Street Hospital for Sick Children in London. At the time this was the leading institution in the world for not only pediatric care but also the education of practitioners in the field. Dr. Lewis was inspired to bring what he saw in London to the United States. Lewis and his colleague Dr. Hewson Bache begin to work on what has now become the Children's Hospital of Philadelphia.

In 1855, the Children's Hospital of Pennsylvania (CHOP) in Philadelphia opened its doors. By 1871, CHOP was performing its first pediatric surgeries, and in 1871 the first pediatric-centered medical training program was established. Surgical clinics were created to train surgeons who were now working at the few emerging children's hospitals across the country. As early as the 1870s, physicians at the Children's Hospital of Philadelphia pressured the lay trustees who managed the hospital to increase patient

turnover and accept more acutely ill children, especially orthopedic surgical patients who had something to offer physician education and on whom new surgical techniques and therapies could be tried. This new emphasis on the medical needs of patients and the experimental needs of doctors and nurses conflicted with the social welfare role children's hospitals saw themselves as performing. Medical staff members at CHOP have been at the forefront of innovation for decades, and their work has had impacts which can be seen to this day, in the form of the Isolette Incubator, the Measles vaccine, and its participation in The Human Genome Project (Fig. 1).

The Children's Hospital in Boston was the second such specialty hospital in the United States and admitted its first patient in 1869. By the 1920s and 1930s, The Children's Hospital in Boston was becoming a major center for advanced care of the pediatric patient while also performing novel and innovative procedures for the first time. Advancements at The Children's Hospital in Boston have continued to the present day and it remains a distinguished center; notable accomplishments include the first correction of hypoplastic left heart syndrome (1983) and the first pediatric open-heart transplant (1986).

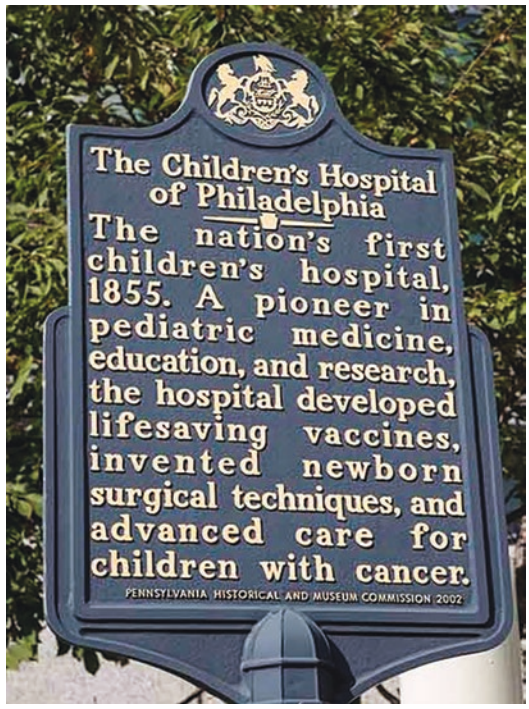

Fig. 1 Placard commemorating founding of The Children's Hospital of Philadelphia in 1855

Surgical Pioneers in Pediatric Surgery

William E. Ladd is often referred to as the *father* of pediatric surgery. A Harvard-educated physician, Dr. Ladd's career path was dramatically altered after being dispatched by US President Lowell to treat the approximately 9000 victims who were innocent bystanders at the accidental collision of two ships in the Halifax Harbour in Nova Scotia in 1917. The explosion was the most powerful nonnuclear explosion that had ever occurred in history, and 4% of the population of Halifax was killed instantly. Dr. Ladd was sent on one of the first trains deployed to the accident site in Nova Scotia, and his experiences in Halifax had a profound effect upon him. After returning to Boston, Dr. Ladd devoted himself entirely to the surgical care of infants and children. Dr. Ladd recognized that children needed a very gentle and thorough physical evaluation, and surgeons needed to rely upon their own senses. Additionally, adult surgical instruments were not suitable for children, and he began to develop appropriately sized instruments (Fig. 2).

In 1918, Dr. Ladd became an instructor in surgery at Harvard Medical School, and by 1927, he was named the chief of surgery. In 1931, Dr. Ladd became a full Harvard Medical School Professor, and in 1941, he published the seminal textbook entitled *Abdominal Surgery of Infancy and Childhood*. As quoted by Donald Watson, "Dr. Ladd brought the diagnosis and management of surgical lesions of infancy and childhood into new perspective." Indeed Dr. Ladd's pioneer efforts truly initiated pediatric surgery as a separate discipline in the Western Hemisphere. Physicians who trained under Dr. Ladd in Boston perpetuated the specialty and achieved their own independent successes to further cement and validate the emerging specialty. These physicians included Drs. Robert E. Gross, Theodore Jewett,

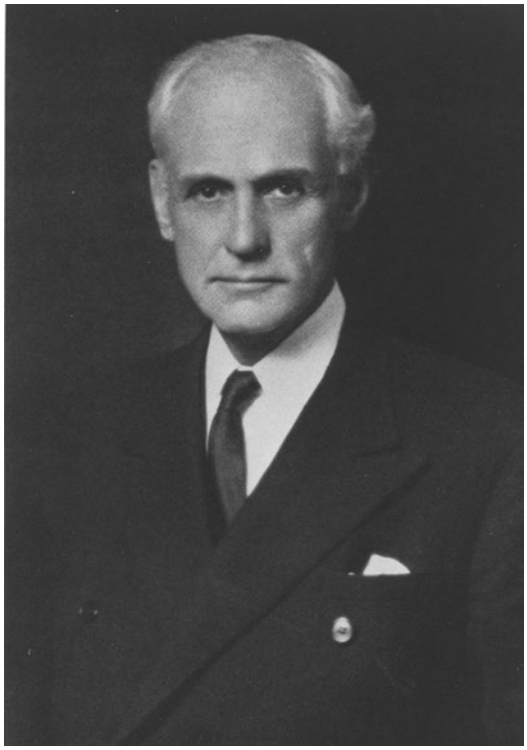

Fig. 2 William E. Ladd, M.D., founder of pediatric surgery in the United States

Earle Wrenn, Donald Rooney, C. Everett Koop, and Monford Custer—all of them continued to advance the field of pediatric surgery in the twentieth century.

Origins of Pediatric Anesthesiology

The subspecialty of pediatric anesthesia has significantly evolved since its origin in Jefferson, Georgia, when Dr. Crawford Long administered the first documented ether anesthetic to an 8-year-old boy for a toe amputation on July 3, 1842. From the very beginning, it was clear that children were at higher risk than adults for anesthesia-related complications and death because of differences in their physiology, anatomy, and functional development. The progression of pediatric anesthesia as a subspecialty arose from the evolution of pediatric surgery. The history of pediatric anesthesia is intertwined with Dr. William Ladd's advances in pediatric surgery and his work in creating the subspecialty Children's Hospital of Boston.

Prior to World War II, two anesthesiologists played a pivotal role in establishing pediatric anesthesia's role as an important necessity for successful surgery in pediatric patients. Dr. Charles H. Robson from Toronto's Hospital for Sick Children was perhaps the first pediatric anesthesiologist. Dr. Robson's practice of administering open-drop ether and cyclopropane and his use of tracheal intubations in children in the 1930s demonstrated early clinical applications of his research in pediatric anesthesia (Fig. 3).

Dr. Philip Ayer working in England during the same period contributed to the development of the "T-piece" as part of the breathing circuit. Post-World War II, a group of six anesthesiologists around the world played key roles in further refining the role of the pediatric anesthesiologist. In Boston, Dr. Robert M. Smith's invention of the precordial stethoscope was groundbreaking, and in Philadelphia Dr. Margo van Deming developed tools to determine anesthetic blood levels in

Fig. 3 Dr. Charles Robson, Pioneer Canadian pediatric anesthesiologist. (Reprinted with permission. Pediatric Anesthesia, Volume: 22, Issue: 3, Pages: 275–277, First published: 24 October 2011, DOI: 10.1111/j.1460-9592.2011.03724.x)

infants. Dr. Digby Leigh, based out of Montreal and Los Angeles, and Dr. Jackson Rees further refined pediatric breathing apparatus. Meanwhile in New York City, Dr. Virginia Apgar developed infant scoring systems to determine neonatal well-being immediately after birth. Finally, Dr. Smith's first pediatric anesthesia textbook is among the pioneering influences that helped shape the early phases of pediatric anesthesia.

The aforementioned events coincided with the elevation of anesthesiology to a specialty rank distinct and equal to surgery and medicine, with its own specialty board (established in 1937) and training programs. By 1941, the American Board of Medical Specialties (ABMS) approved the American Board of Anesthesiology (ABA) as a separate primary board. In the 1960s and 1970s, pediatric anesthesia entered into its first explosive period of growth fueled by translational discoveries in human biology, including fundamental understandings of the transition from fetal to postnatal circulation. Research on homeostatic fluid regulation, electrolytes, metabolism, temperature regulation, monitoring of blood gases, mechanical ventilation, and cardiopulmonary resuscitation helped in developed neonatal and pediatric care that previously did not exist.

The 1980s and 1990s were transformative years that witnessed the establishment of pediatric anesthesia as a formal subspecialty fellowship training programs implemented across the United States. In 1997, the American Council on Graduate Medical Education recognized pediatric anesthesia as subspecialty, and pediatric anesthesiology falls under its purview. In 2012, the ABMS approved the ABA's time-limited pediatric anesthesiology subspecialty certificate for physician credentialing.

Developments Leading to Pediatric Heart and Congenital Surgery

The development of pediatric cardiac and congenital surgery arose from the confluence of multiple events. At the very basis of the field was the initial descriptive study of pediatric cardiac defects—many of which were acquired from birth or deemed to be *congenital*. In the early 1600s, a group of anatomists published vastly descriptive accounts of the pediatric cardiac anatomy and vasculature. Dr. Lee Harvey published *De Motu Cordis*, an account of the pulmonary and systemic circulations. In 1671, Niels Stenson of Copenhagen described the cardiac pathology of a stillborn fetus with multiple congenital anomalies including the cardiac lesion, which is now recognized as tetralogy of Fallot. Dr. Stenson correctly described the physiologic consequences of the anatomic malformation. More than 100 years later, Dr. Edwardo Sandifort, for the first time, described the clinical symptoms of a young child whom he called "blue boy." Because the child had appeared normal at birth, he suspected that the condition was acquired, but when he died at twelve and one-half years of age, it was apparent, at postmortem study, that this was a congenital defect, which included a patent foramen ovale, a small pulmonary artery with a blocked pulmonary valve, and a ventricular communication between the two ventricles. In 1888, the anatomic lesion, now called tetralogy of Fallot, was named for Etienne-Louis Fallot who stated that 75% of patients with cyanotic heart disease would have either pulmonary stenosis or atresia, an overriding aorta, a ventricular septal defect, and right ventricular hypertrophy; his assertions were validated by autopsy findings.

Clinicians who advanced the study of pediatric cardiology began to manifest their findings by the early 1800s. In 1819, Rene Laennec developed the stethoscope, and this allowed physicians to begin to relate murmurs heard by auscultation and correlate them to pathologic findings found at autopsy. In the 1850s, Thomas Peacock noted the characteristic radiation of the murmur of pulmonary stenosis. In 1858, he published a book that contained beautiful illustrations of various congenital malformations, including descriptions of ventricular septal defects, pulmonary stenosis, and transposition of the aorta and pulmonary artery. By 1874, Henri Roger described a loud murmur accompanied by a thrill to be pathognomonic of a communication between the two ven-

tricles that was compatible with a long life. Gibson described the murmur as well as the pathophysiology of patent ductus arteriosus in 1898.

In 1930, Dr. Helen Taussig was placed in charge of the cardiac clinic at the Harriet Lane Home for Invalid Children in Baltimore, Maryland, and had a fluoroscope installed. Helen Taussig learned to utilize the fluoroscope so that she might learn more about congenital malformations of the heart. Using both electrocardiogram and fluoroscopy, Taussig was able to correlate physical findings with the pathology noted at autopsy. Dr. Taussig's descriptions of anatomic lesions corroborated with fluoroscopy led to the final crucial knowledge needed to provide surgeons with conclusive evidence that would warrant a surgical approach. In 1938, Dr. Robert Gross ligated the patent ductus of a patient, and thus the discipline of pediatric cardiology and cardiac surgery was born.

A few physicians recognized that infants with Tetralogy of Fallot were often pink until the ductus arteriosus closed. Dr. Taussig hypothesized that if a patent ductus could be ligated, then why not surgically construct a ductus. Taussig initially approached Dr. Gross to attempt such a procedure but he declined; however, she found another surgeon, Alfred Blalock, to possibly consider such an operation. Blalock had already performed anastomoses between the left subclavian artery and pulmonary artery in his attempt to learn more about pulmonary artery hypertension. In November 1944, Blalock anastomosed the left subclavian artery to the pulmonary artery; this positively impacted the life of a severely cyanotic child with tetralogy of Fallot. The Blalock-Taussig operation, as it was named, soon had worldwide recognition. The following year, Crayfoord and Nylin from Stockholm, Sweden, successfully repaired a coarctation of the aorta with an end-to-end anastomosis. All of these surgical procedures were performed on the beating heart. To repair intracardiac lesions, cardiopulmonary bypass was necessary. In 1955, Walt Lillehei and colleagues in Minneapolis reported the results in 32 patients with ventricular septal defect, tetralogy of Fallot, and atrioventricular communis defects using a human cross-circulation technique.

The arrival of a mechanical cardiopulmonary bypass device was not an overnight event, and it took a long series of events to occur prior to the arrival of the "heart-lung" machine to be invented. An Austrian-German physiologist, Maximilian von Frey, developed an early prototype of a heart-lung machine in 1885 at the University of Leipzig. However, the utilization of this machine was not feasible before the discovery of heparin in 1916 which was necessary to prevent clotting of the mechanical components within the device. A Soviet scientist Sergei Brukhonenko developed a heart-lung machine for total body perfusion in 1926 which was used in experiments with canines. Dr. Clarence Dennis led the team that conducted the first known operation involving open cardiotomy with temporary mechanical takeover of both heart and lung functions in 1951 at the University of Minnesota Hospital; the patient did not survive due to an unexpected complex congenital heart defect. This followed 4 years of laboratory experimentation with dogs with a unit called the *Iron Heart*. A team of scientists at Birmingham University (including Eric Charles, a chemical engineer) were among the pioneers of this technology. Another member of the team was Dr. Russell M. Nelson, who performed the first open-heart surgery in Utah.

The first successful mechanical support of left ventricular function was performed in July 3, 1952, by Forest Dewey Dodrill using a machine, the Dodrill-GMR, codeveloped with General Motors. The machine was later used to support right ventricular function. The first successful open-heart procedure on a human utilizing the heart-lung machine was performed by John Gibbon in 1953 at Thomas Jefferson University Hospital in Philadelphia. He repaired an atrial septal defect in an 18-year-old woman. Dr. Gibbon's cardiopulmonary bypass machine was further developed into a reliable instrument by a surgical team led by John W. Kirklin at the Mayo Clinic in Rochester, Minnesota, in the mid-1950s (Fig. 4).

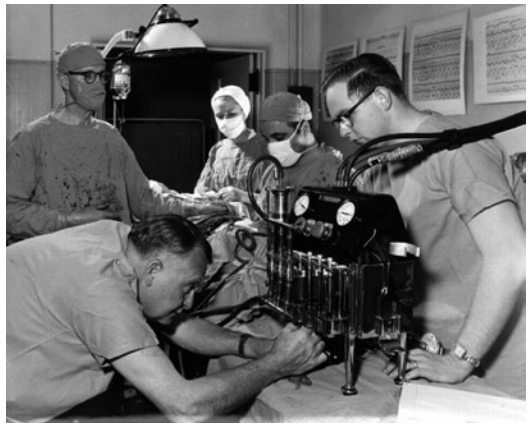

Fig. 4 The Dodrill-GMR heart pump. (Dr. Dodrill is in scrub cap and mask on the left. Used with permission from Dr. William S. Stoney. Adapted from Stoney WS. Historical perspectives in cardiology. Circulation 2009; 119: 2844–53)

Future Directions

As a medical specialty, pediatric cardiology and pediatric heart/congenital surgery have always required a multi-disciplinary team—pathologists, physiologists, cardiologists, surgeons, intensivists, interventionalists, and anesthesiologists—each playing a critical and pivotal role in the treatment of children with cardiac congenital disease. In the twenty-first century, geneticists, molecular biologists, and other basic scientists are contributing their innovative discoveries to this diverse team to ensure new discoveries and advances for pediatric cardiology and children yet to be born. The amalgamation of specialties with seemingly divergent interests is now allowing the formation of "hybridized" environments where multidisciplinary teams create new procedures combining elements of traditional open-heart surgery with minimally invasive techniques. New techniques in DNA sequencing will allow early recognition of genetic disorders predisposing individuals to congenital cardiac disease. Minimally invasive techniques will continue to play a larger role in the repair of congenital lesions either in utero or post-delivery in the neonatal period. Additionally, the role of three-dimensional computer imaging, reconstruction and printing will play a pivotal role in addressing treatment of structural congenital defects. The traditional "operating room" of the twenty-first century will continue to evolve and transform into a complex array of medical and surgical specialists working alongside with basic scientists in a state-of-the-art environment to allow translational endeavors to flourish.

Useful Resources: (Noonan 2004; Mai and Coté 2012; Costarino and Downes 2005; Mai et al. 2013).

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Cardiovascular System Embryology and Development

Ali Dabbagh, Abdollah Amini, Mohammad-Amin Abdollahifar, and Mohammad Ali Saghafi

Abstract

During the embryonic period, the heart is the first organ that is formed and starts functioning; this stage is the time that the embryo could not support its nutritional requirements just by the "***simple diffusion from the placenta*** anymore "; so, the heart appears as a new organ. However, the development of the cardiovascular system is not a simple task and several timely mannered developmental steps are necessary to create cardiovascular structures, with appropriate functions and spatial configuration, including right-left direction. Any genetic, epigenetic, environmental, or other forms of unplanned perturbation could potentially lead to congenital cardiovascular disease. In this chapter, the development of the heart and vascular system is discussed, embedded with *Clinical note* which cite some of the related congenital heart disorders.

Keywords

congenital heart disease · Embryology Development · cardiovascular system

Establishing Cardiac Crescent

According to Kloesel et al., there are nine separate steps in the development of the cardiovascular system (Kloesel et al. 2016):

1. Gastrulation.
2. Primary and Secondary heart fields.
3. Development of the heart tubes.
4. Cardiac looping and is related steps.
5. Septation and cardiac chambers.
6. Outflow tract development.
7. Cardiac valve development.
8. Development of the cardiac vasculature.
9. Development of the cardiac conduction system.

The human zygote is created from the fusion of an oocyte and a sperm, being the first cell of a new individual that starts the mitotic divisions, that is, the cleavages immediately afterward (Tosti and Ménézo 2016). The single-celled zygote is developed to the 16-celled morula, which enters the uterine cavity about the fourth developmental day (Ferrer-Vaquer and Hadjantonakis 2013) and then undergoes cell division, compaction, and cavi-

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tation to form the human blastocyst (Pfeffer 2018). Further blastocyst development includes the following steps:

- uterine implantation,
- formation of two layers (epiblast and hypoblast) from the inner cell mass,
- formation of the primitive streak which is a groove in the epiblast starting from the caudal part, and extending to the cranial region; at this point, the cells proliferate to form the primitive knot (primitive node),
- ingression of epiblast cells throughout primitive streak which leads to the formation of three germ layers including endoderm, mesoderm, and ectoderm layers.

Myocardial progenitor cells come out of the anterior splanchnic mesoderm. These myocardial progenitor cells start their development process through four "sequential but at times, overlapping" stages (Wu et al. 2006; Abu-Issa and Kirby 2007; Lin et al. 2012; Brade et al. 2013):

1. cardiogenic ***mesoderm*** specification,
2. bilateral ***establishment*** of heart fields,
3. composition and configuration of the ***heart field***,
4. differentiation of cardiomyocyte and formation of the ***heart tube***.

As noted, the heart originates from the anterior splanchnic mesoderm. However, parts of the endoderm are involved in the development of the heart; to form the endodermal portions of the heart, these endodermal parts are enveloped by mesoderm (Buijtendijk et al. 2020; Swedlund and Lescroart 2020).

The cardiac progenitor cells develop locally into the splanchnic layers of the lateral mesoderm on both left and right sides of the embryo to form bilateral blood islands in the splanchnic mesoderm, leading to **cardiogenic mesoderm specification**. Also, blood islands appear bilaterally in this mesoderm, which will later form blood cells and two dorsal aortae (Gittenberger-de Groot et al. 2005; Sato 2013; Cao et al. 2020).

In the next stage, after the development of the cardiac progenitor cells in the lateral mesoderm, two "lateral mesodermal islands" or "lateral cardiogenic plates" are created, which eventually fuse in the midline to form the *cardiac crescent* which has the following features (Yutzey and Kirby 2002; Lockhart et al. 2011; Sato 2013):

- it has an "arch-shaped" or "bow-shaped" or "horseshoe-shaped" feature in the caudal part of the embryo,
- it constitutes the so-called **primary heart field or first heart field** (PHF or FHF); on days 16–18,
- then, PHF gives rise to some of the main structures of the mature heart: atria, left ventricle, atrioventricular (AV) canal, and most of the right ventricle (Fig. 1).

PHF has two poles with the following order in migration and looping:

- a cephalad pole, which will later constitute the bulbos cordis and aortic roots (i.e., the outflow tract),
- the caudal pole, which is also known as the sinus venosus, will later constitute the ventricles and the ends of those major veins that bring the venous blood to the heart; also, some segments of the atria are made from the caudal pole (Lin et al. 2012).

While the cardiovascular system forms in about the middle of the third week, this primary heart tube has rhythmic peristalsis activity by the end of the third week. After rightward looping of the primary heart tube, these two poles of the primary heart tube are changed accordingly:

- anterior specification: ventricular segments,
- posterior specification: atrial segments.

During later stages of cardiac development, another important part named **secondary heart field** (SHF) is created with the following characteristics (Moorman et al. 2003; Verzi et al. 2005; Restivo et al. 2006; Watanabe and Buckingham

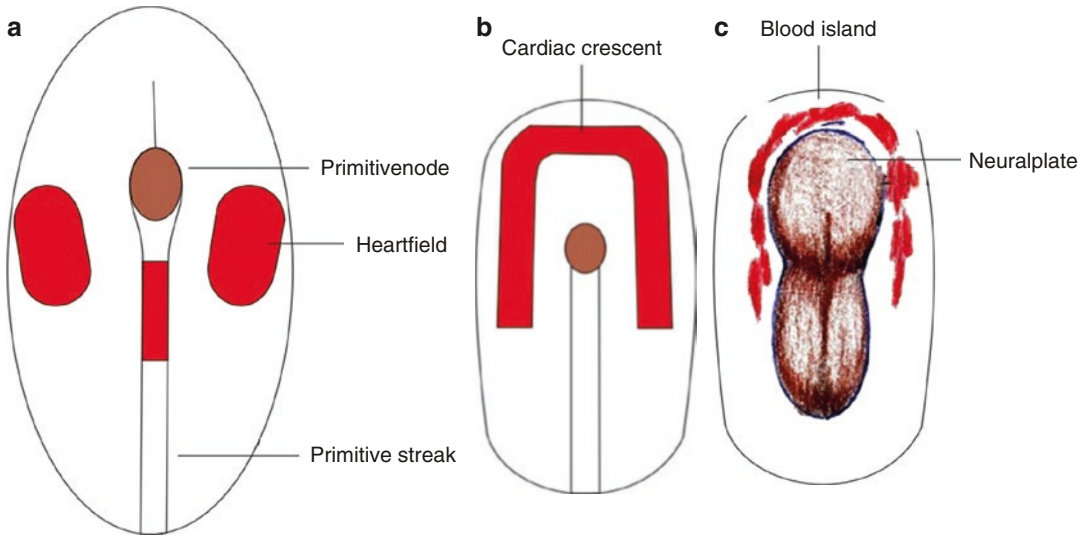

Fig. 1 Early development of the heart; (**a**, **b**, and **c**) Dorsal view of an embryo. Hemangioblasts reside in the splanchnic mesoderm in front of the neural plate and on each side of the embryo

2010; Xin et al. 2013; Kelly et al. 2014; Calkoen et al. 2016; Cortes et al. 2018):

- SHF is "a second cellular pool".
- It is derived from the *ventral pharyngeal splanchnic mesoderm.*
- SHF is located medial and anterior to the cardiac crescent (i.e., medial and anterior to PHF and dorsal to the primary heart tube).
- Its main function is to give cellular origin to "the arterial and venous side of the heart".
- SHF, during days 20 and 21, primarily gives origin to the conotruncal region of the heart, which includes mainly the following segments in the mature heart: other primordial parts of the right ventricle, interventricular septum (IVS), the endothelial and myocardial components of ***the outflow tract*** (i.e., conotruncus) (Kelly et al. 2014; Kloesel et al. 2016).
- Another major function of the SHF is the laterality of cardiac constituents; laterality is defined as a left-right body axis which is an integral and basic component of the embryonic development, leading to the defined organ asymmetries in the adult organism; the cardiovascular system is one of the most prominent presentations of the laterality in the human body (Kelly et al. 2014; Kloesel et al. 2016).

Clinical note:
Some of the most common congenital heart disorders due to conotruncal defects are:
- Persistent truncus arteriosus
- Tetralogy of Fallot (TOF)
- Double-outlet right ventricle
- Pulmonary atresia
- Pulmonary stenosis (Restivo et al. 2006)

Formation of the Heart Tube

The heart arises from a common mesodermal pool of progenitor cells; which is part of the cardiopharyngeal region. During the early phases of cardiac development, some parts of the primary cardiogenic area are anterior to the neural tubes; however, due to the very rapid growth of brain vesicles, there is a cephalad movement of the oropharyngeal membrane, which, in turn, pushes the heart into the more caudal parts; then, the heart comes to an inner position to be part of the future thorax. From another point of view, the oropharyngeal region becomes compressed in between the brain, the yolk, and the heart (Soukup et al. 2013; Diogo et al. 2015).

The process of body folding involves both cephalocaudal and lateral folding of the embryonic plate. As the embryonic plates fold laterally, the endocardial tubes fuse to form a heart tube;

by this process, the heart tube is gradually formed (Yutzey and Kirby 2002; Abu-Issa and Kirby 2007).

Usually, "**looping of the heart tube,**" which is discussed in the next paragraphs, is considered as the primary visible sign for asymmetry during embryo development. However, the formation of the atrioventricular canal is structurally asymmetric associated with left-sided bulging (Moorman et al. 2003).

Therefore, the heart tube is composed of three distinct layers (Yutzey and Kirby 2002; Lockhart et al. 2011):

1. The inner endothelial cover; that is, *endocardium* (which lines the inner layer of the heart tube).
2. The outer myocardial layer; that is, *myocardium*; the endocardium and myocardium are separated by an acellular space which is rich from the extracellular matrix (ECM); this thick ECM, also named "***cardiac jelly***" is secreted by the myocardium and is rich in some specific molecules including hyaluronic acid, hyaluronan, fibronectin, fibrillin, proteoglycans, and collagens which have important roles in heart development; especially for proper development of endocardial cushion of the atrioventricular junctions.
3. The epicardium (visceral pericardium) is derived from mesodermal cells that arise from splanchnic mesoderm on the surface of the septum transversum and sinus venous which migrate onto the outer surface of the myocardium.

During later developmental phases, the heart tube becomes swelled and progressively invaginates into the pericardial cavity. At first, it is attached to the dorsal wall of the body through the dorsal mesocardium which is a fold of mesodermal tissue (Moorman et al. 2003; Lin et al. 2012). However, the central portion of the dorsal mesocardium degenerates and forms the transverse pericardial sinus, which is located between the left and the right sides of the pericardial cavity (Fig. 2).

The heart is now attached only at its caudal and cranial parts in the pericardial cavity by blood vessels; that is, the ventricular loop of the heart has gained both "inlet and outlet components". The inflow to the heart is initially supplied by three pairs of drainage veins into the tubular heart through vitelline veins (return poorly oxygenated blood from the umbilical vesicle), umbilical veins (carry well-oxygenated blood from the chorion), and com-

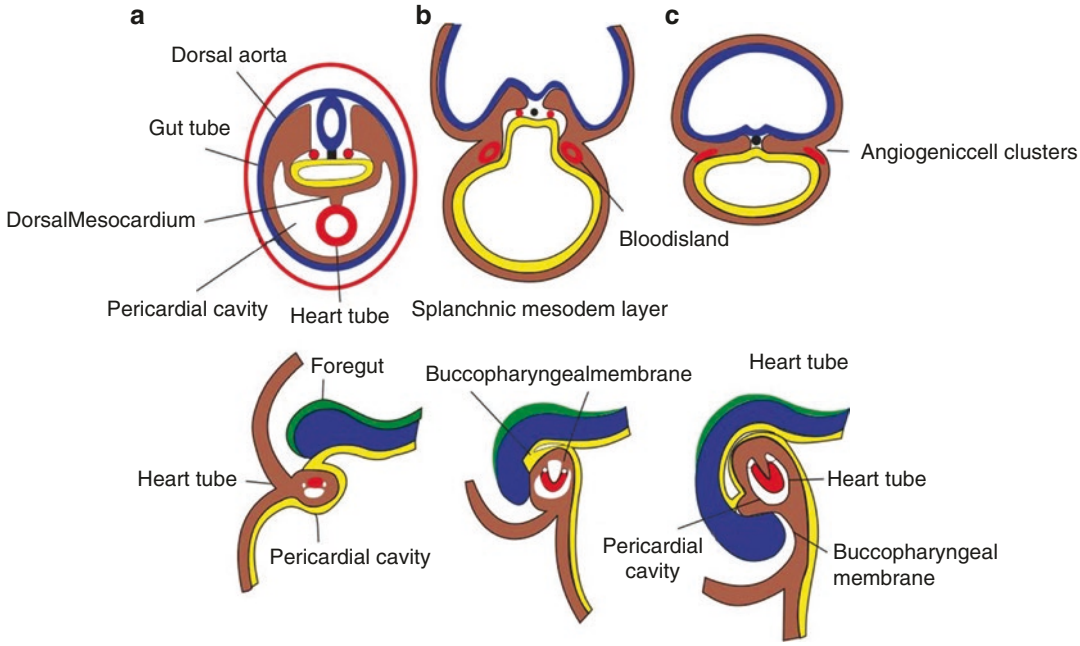

Fig. 2 Transverse sections and longitudinal section through embryo at different stages of heart tube formation; (**a**) 17 days; (**b**) 18 days; (**c**) 22 days

mon cardinal veins (return poorly blood with low oxygen from the embryo body) (Moorman et al. 2003; Lin et al. 2012). On the other side, the outlet supports the cardiac outflow tract; it means that the left and right dorsal aortae make the outflow of the heart vessels, which in turn leads to arteries emerging from the aortic sac and then going to pharyngeal arcs. In the area of the arches, the dorsal aortae are arranged as paired vessels, but caudal parts of the dorsal aorta join together to form a single aorta (thoracic aorta and abdominal aorta).

However, with improvements in heart development, the heart loop is completed and expands; the dorsal mesocardium breaks up, except in the most caudal segment which plays the role of venous pole for the heart; this dorsal mesenchymal part has a central role in some major events of heart development like pulmonary vein development and atrioventricular mesenchymal complex formation.

The Looping of Cardiac Tissue

The primitive heart tube begins to elongate on day 23; however, the signaling pathway guaranteeing right-sided looping is initiated earlier. It means that the looping process is signaled during gastrulation; as mentioned earlier, "**looping of the heart tube**" is the primary visible sign for asymmetry during embryo development. The process of the cardiac loop is completed by day 28 (Yutzey and Kirby 2002; Moorman et al. 2003; Jacobs et al. 2007).

As the primitive heart tube elongates in both cranial and caudal parts, the dorsal mesocardium is detached from the developing left ventricle, leading to the liberation of the heart tube. The heart tube bends rightward after its liberation (Moorman et al. 2003).

Then, in the process of looping, the ***cephalic part*** of the heart tube bends in three directions:

- ventral,
- caudal,
- to the right.

However, the ***caudal part*** itself bends again and extends in these three directions:

- dorsal,
- cranial,
- to the left.

As mentioned before, these processes of bending are completed by day 28 and lead finally to the "***cardiac loop.***"

Over the next five weeks, a series of "strictures" and "bulged areas" are created in the primitive heart tube. Through the bulged regions, the following structures come out:

- bulbus cordis (which includes truncus arteriosus, conus arteriosus, and conus cordis),
- ventricle,
- atrium,
- sinus venosus.

The resultant "ventricular loop" has two main components:

- the inlet: gives origin to the sinus venosus; which starts at the caudal end and consists of left and right sinus horns; these right and left horns are partially confluent; also, the common cardinal veins drain into sinus venosus (Yutzey and Kirby 2002),
- the outlet: consists of the conus and truncus and the arterial system (including the aorta and pharyngeal arcs) originate from the outflow tract SHF is the origin of the outflow tract myocardium which comes out of the ventricular outlet; (Restivo et al. 2006; Watanabe and Buckingham 2010).

Two other chambers are cranial to sinus venosus: these are:

- **the primitive atrium**: which will form the common atrium (also known as primitive atrium); this primitive atrium will form the left and the right atria,
- **the primitive ventricle**: which will form the left ventricle; however, the primitive ventricle is separated from the next expansion (i.e., the bulbus cordis) by the bulboventricular sulcus; the latter segment will form much of the right ventricle.

Conotruncal segment: the distal outflow tract of the right and left ventricles has the same origin. The **conotruncal segment** is the cranial-most segment of the ventricles and forms the following parts:

- outflow tract: the distal outflow region of each of the left and right ventricles,
- conus cordis (or conus arteriosus): after creating the outflow tract, the conotruncal segment is further subdivided into the conus cordis (or conus arteriosus), and the truncus arteriosus; conus cordis will be eventually incorporated into the corresponding right and left ventricles,
- truncus arteriosus: this is the third part of the conotruncal segment and splits into two parts to form the pulmonary artery and the ascending aorta; however, the most cranial end of the truncus arteriosus is connected to a dilated expansion called **the aortic sac** (Fig. 3).

The aortic sac is continuous with the first aortic arch and, eventually, with the other four aortic arches. The aortic arches from major arteries transport blood to the head and also, to the trunk. On the other hand, the sinus venosus receives blood from the common cardinal vein, the umbilical vein, and the vitelline vein that bring the

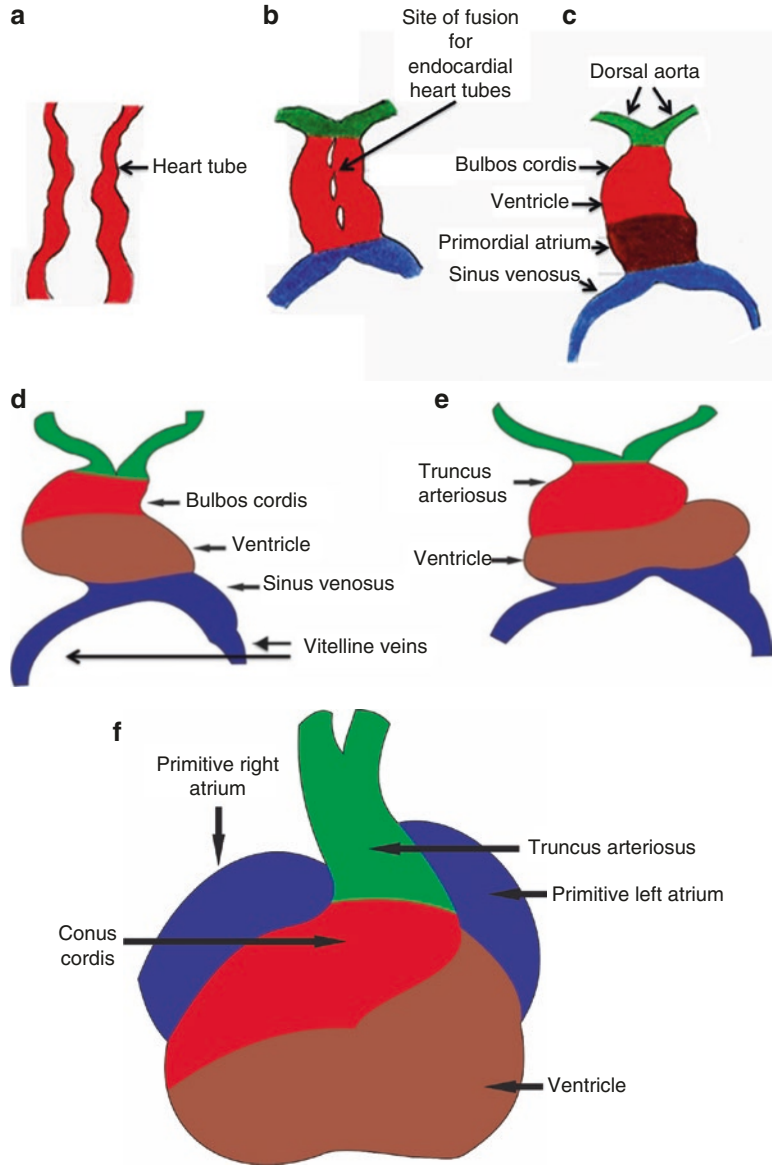

Fig. 3 Developing of the cardiac loop. (**a**) 18 days. (**b**) 22 days. (**c**) 23 days. (**d**) 24 days. (**e**) 28 days. (**f**) 35 days

blood back to the heart from the chorion, the umbilical vesicle, and the embryo, respectively.

Clinical note:
In the case of abnormal looping, there may be:
Random looping
- Anterior looping
- Leftward looping

In the clinic, abnormal looping could be seen in the following clinical syndromes:
- Abnormal atrial situs (situs inversus or isomerism)
- Dextrocardia
- Ventricular inversion

We never see heterotaxia patterns in ventricles; heterotaxia is exclusively seen in the atria of the heart (Gittenberger-de Groot et al. 2005; Jacobs et al. 2007)

The Formation of the Sinus Venosus

At the end of the fourth week, the heart contracts synchronize and led to the moving of the blood in one direction. During this time, the venous blood from the right and left sinus horns enter to sinus venosus. Usually, three important veins enter the right and left horns that including (1) embryo via the common cardinal veins; (2) developing placenta via the umbilical veins, and (3) umbilical vesicle via the vitelline vein. The primordial atrium receives blood from the sinus venosus under the control of sinoatrial valves. The blood then enters into the primordial ventricle through the atrioventricular canal. Simultaneously, with the contraction of the ventricle, the blood is pumped via the bulbus cordis and truncus arteriosus and enters into the aortic sac. The blood then distributes to the embryo, umbilical vesicle, and placenta through the dorsal aortas. Initially, the opening between the atrium and the sinus is big. Soon, however, the sinus entrance shifts to the right side. This shift is affected primarily by left-to-right shunts of blood, which take place in the venous system during the fourth and fifth weeks of development (Fig. 4).

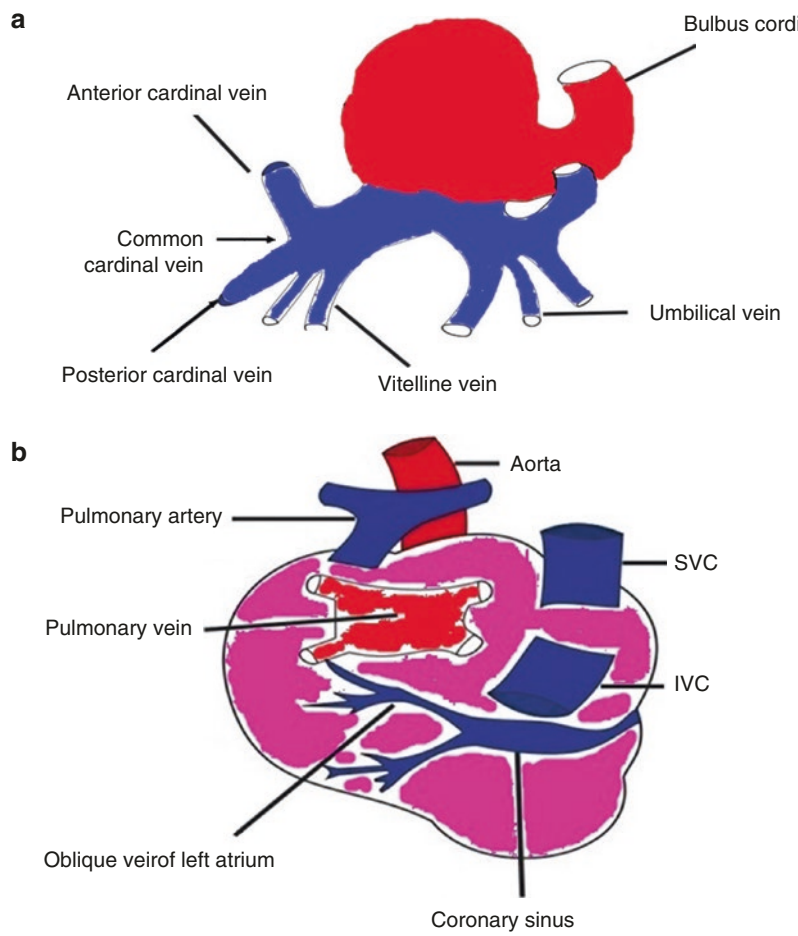

Fig. 4 Different stages of development in "sinus venosus"; (**a**) 24 days; (**b**) 35 days

The Next Steps in Differentiation: Atrial Development

Blood flow from left to right causes enlargement of the right sinus and right-sided veins. The right horn is the main confluence between the original sinus venosus and the atrium; this right horn develops gradually into the right atrium and makes the smooth part of the right atrial wall. Now, the sinoatrial orifice is edged on each side by a valvular fold; these folds will create ***the right and the left venous valves***. After a while, the dorsocranial parts of these valves fuse; the result is the formation of a ridge called ***septum spurium*** (Fig. 5a).

In the next stage, the right sinus horn is merged into the atrial wall; however, the left venous valve and the septum spurium fuse with the atrial septum. Meanwhile, all of the superior parts of the right venous valve are drawn back, but the inferior parts are changed into two parts: the inferior vena cava (IVC) valve and the coronary sinus valve (Fig. 5b).

As mentioned in the previous segments, during the development of the heart, the heart segments are arranged from cephalad to caudal as the order (Fig. 3d):

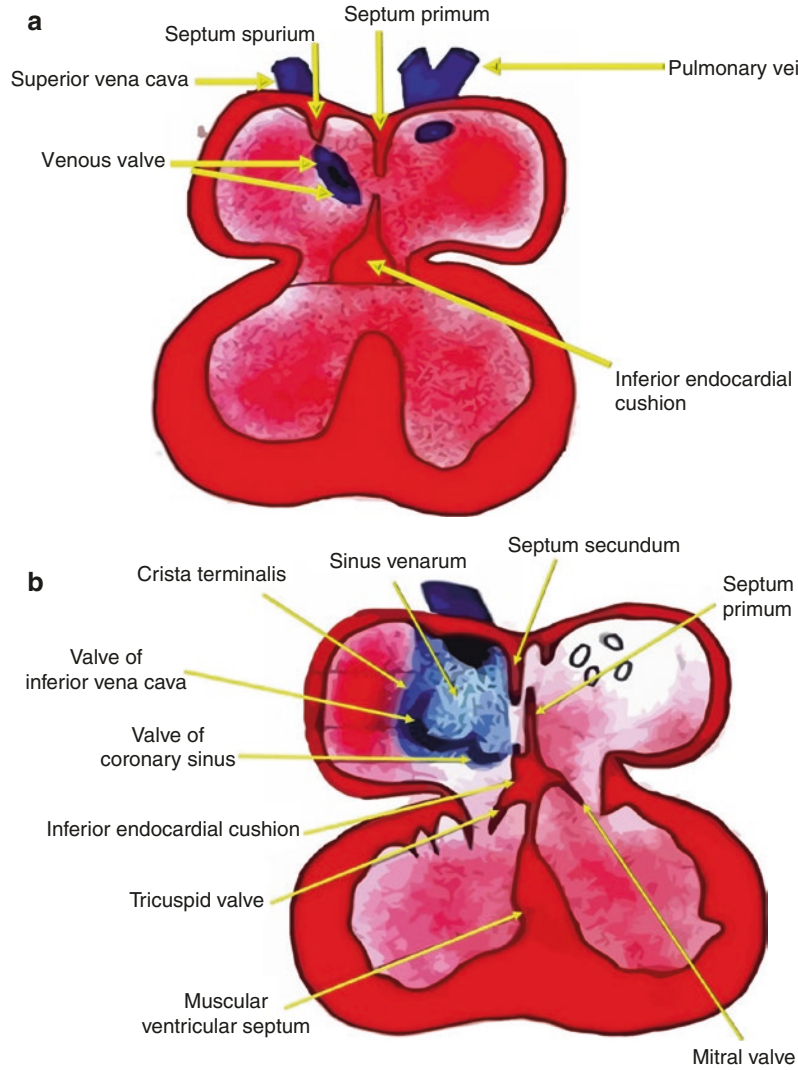

Fig. 5 Coronal sections of the heart at the atrioventricular canal level; (**a**) five weeks; (**b**) Fetal stage

- vitelline veins,
- primitive atrium,
- sinus venosus,
- ventricle,
- conotruncal segment (including outflow tract, bulbos cordis, and truncus arteriosus).

However, sinus venosus is located between vitelline veins (cephalad) and the primitive atrium chamber (caudad). Sinus venosus persists until adulthood when sinus venosus forms the smooth-walled parts of the right atrium; in mature heart, this smooth part of the right atrium is called "**sinus venarum"** or "**venarum sinus,"** which composes the main parts of the posterior atrial wall and the majority of the interatrial septum and the lateral wall of the right atrium; in adult heart, sinus venarum surrounds the openings of the venae cavae and the coronary sinus (Taylor and Taylor 1997; Ho et al. 2002).

There is a junction between the sinus venosus and the primary atrium which is called "**crista terminalis"** (Fig. 5b); in the mature heart, crista terminalis is a fibromuscular ridge at the posterolateral region of the right atrium. Crista terminalis is the anatomical margin between the anterior wall of the right atrium (i.e., the trabeculated-walled right atrium which contains pectinate muscles and the right atrial appendage) and the posterior wall of the right atrium (i.e., the smooth-walled parts of the right atrium also named sinus venarum) (Freedom et al. 2005).

Clinical note:
Crista terminalis functions as the anterior pathway for typical atrial fibrillation or atrial flutter. Also, in some patients, crista terminalis could mimic the right atrium masses in echocardiographic exams; especially in patients with supraventricular arrhythmias; in which a suspicious mass in the right atrium is of utmost importance and needs vigilance for differential diagnosis; in such patients, sophisticated transesophageal echocardiography and/or cardiac computed tomography/magnetic resonance imaging are needed to rule out the differential diagnosis (Ellis et al. 2000; Gaudio et al. 2004; Akcay et al. 2007; Salustri et al. 2010; Na et al. 2011; Siddiqui et al. 2013; Nakanishi et al. 2015)

The primary atrium starts to be formed at about two weeks of gestation. As the primitive atrium enlarges, it partially envelops the bulbus cordis; meanwhile, the right atrium and the left atrium are created out of the primary atrium mainly due to the growth of the septum primum:

- the primitive right atrium is created out of the primitive atrium by fusion of the right sinus horn; as mentioned above, the right atrium consists of two main parts, the trabeculated right atrial appendages which gives origin to pectinate muscle, and the smooth-walled sinus venarum originating from the right horn of sinus venosus; the pectinate muscles cover the entire wall of the right atrial appendage (Ho et al. 2002),
- the primitive left atrium expands according to the following order: first of all, an outgrowth of the posterior left atrial wall develops in the left side of the septum premium to from the primary pulmonary vein (Fig. 5a); this primitive pulmonary vein connects with the veins of the developing lung buds; however, during the next expansion, the pulmonary vein and its branches are merged into the left atrium, making the large part of the smooth wall of an adult left atrium. In the left atrium, there is not such a structure as crista terminalis; so, the mouth of the appendage plays the differentiation role between rough and smooth parts of the left atrium. Only one vein opens initially into the left atrium; however, in the mature heart, four pulmonary veins drain into the left atrium. The left atrial wall is smooth in the majority of its segments; but, a few parts are rough; meanwhile, a much less amount of pectinate muscle is seen in the left atrium compared to the right atrium. In the complied heart, the left atrium originates from the appendage of the trabeculated atrial wall and its roof is adjacent to the aorta and pulmonary artery with its trabeculated surface. On the other hand, the smooth-walled portion covers the majority of the left atrial surface, initiates from the pulmonary vein component, and is continued up to the body and the vestibule of the left atrium; also, the smooth wall includes the superior and posterior walls of the left atrium are composed of the smooth wall that and (Fig. 5a, b) (Ho et al. 2002).

The Primordial Heart Septation

After cardiac looping, the heart, composed of inner endocardial lining and outer myocardial cells, is septated into four main independent regions, which eventually conform to the typical anatomy of the future heart chambers and extracardiac arterial system (Lin et al. 2012):

- the atrium,
- the atrioventricular canal (also contains *endocardial cushions*),
- the ventricle,
- the outflow tract (also contains *endocardial cushions*).

"**Septation"** is a critical transitional stage event in heart development; since during septation, the heart is changed from a *single chamber peristaltic tube* to a *four-chambered pump with unidirectional valves* and specific cardiac routes for blood circulation; also, we should note that in the normal developmental sequence of the heart, cardiac looping is an essential prerequisite for septation; so we will have the following three stages as the logical and subsequent stages which constitute cardiac development:

- cardiac looping,
- septation,
- chamber formation.

Also, septation, though a single stage in cardiac development, takes place at three different anatomic levels; that any defect in each of these levels results in specific lesions; these levels are (Gittenberger-de Groot et al. 2005):

- the atrium,
- the ventricle,
- the arterial pole.

However, myocytes participating in chamber formation are not materially involved in septation (Lamers and Moorman 2002; Lin et al. 2012).

Human heart septation starts at the fourth week and is accomplished by the end of the seventh week and involves two main phases which are composed of sequential events:

- During the ***first phase***, two actively growing tissue masses (known as ridges) advance towards each other, until they fuse and make a septum (Fig. 6a, b). This septum primarily divides the heart lumen **into two main single canals** (Fig. 6a). A similar septum may also be actively shaped by a single mass of growing tissue which will develop till it launches into the opposite side of the lumen (Fig. 6c). Synthesis of extra-cellular matrices and cell proliferation plays a main role in the formation of such tissue masses.
- The ***endocardial cushions*** develop into the conotruncal and atrioventricular parts; *endocardial cushions* are local tissue swellings, made of accumulated "cardiac jelly"; in fact, cardiac jelly is abundant masses of extracellular matrix incorporated between the endo-

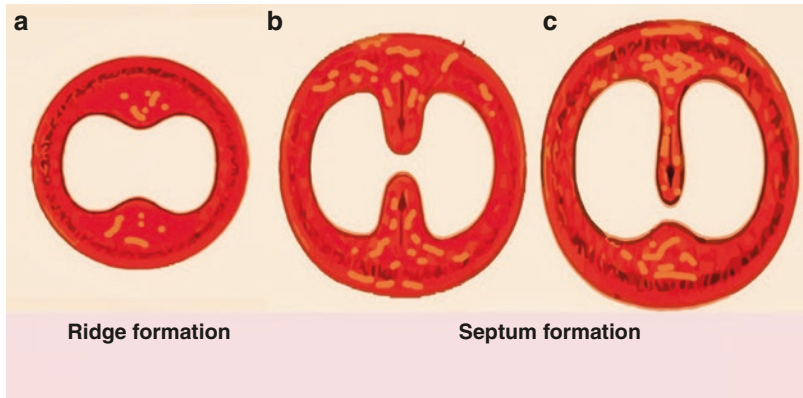

Fig. 6 (**a**) Ridge formation by two actively growing masses; (**b**) Septation and septum formation by two actively growing masses that close to each other until they fuse and make a septum; (**c**) Septation by a single actively growing mass

cardium and the myocardium (Lin et al. 2012). Cardiac jelly is acellular at first; however, after the formation of AV cushions, there is an epithelial-to-mesenchymal transformation (EMT) of the endocardial cells that cover the cushions (Lockhart et al. 2011).

- However, ***endocardial cushions*** when created, participate in the formation of membranous parts of atrial and ventricular septa, the atrioventricular canals, the atrioventricular (AV) valves, and the aortic and pulmonary valves. But, we should remember that endocardium cushions usually do not participate in ***true*** septum formation. Instead, endocardial cushions take part in the septation process in a different way. Their mechanism is that a thin strip of mass tissue in the walls of atria and ventricles grows and spreads around to well expand the surrounding tissue until it makes a thin ridge between two contralateral parts; each of these contralateral thin ridges grow on either side until they reach each other and eventually fuse to form a septum. However, this septation mechanism usually does not completely divide the original lumen; but it leaves a thin link between the two contralateral parts; while later on, the thin canal is endorsed and secondarily supported by the proliferation of neighboring tissues. This mechanism of septation separates the ventricles and atria ***partially*** (Fig. 6a–c). At times, due to this mechanism or other similar mechanisms, some of the cardiac structures are created that are known as ***classic septum*** while they are not real septum and are in fact, ***folds*** or ***layers*** of myocardial tissue that engulf some adipose tissue in between (Anderson et al. 2003a).

Whatever the mechanism of septation, the process of septum formation and cardiac "***chambering***" is not completed until three major subsequent events will happen which eventually will lead to the typical "4 chamber heart":

- creation of the primitive atrial septum (PAS),
- creation of the atrioventricular (AV) cushions which also gives origin into tricuspid valve apparatus and mitral valve apparatus,
- creation of the interventricular septum (IVS).

These three major events are discussed in the next paragraphs.

Septum development in the common atrium: the creation of the primitive atrial septum (PAS).

The septation process in the common atrium starts at the beginning of the fifth week and includes the following steps (McCarthy et al. 2003; Gittenberger-de Groot et al. 2005; Sukernik and Bennett-Guerrero 2007; Asrress et al. 2015; Calkoen et al. 2016):

- a sickle-formed crest derived from the roof of the common atrium grows toward the middle of the heart lumen; this crest makes the first part of the structure called ***septum primum***,
- the caudal end of this septum primum develops towards the fused endocardial cushion which is located in the atrioventricular canal,
- in this stage, there is a gap between two parts of the common atrium which is called the ***ostium primum,*** and allows blood flow between the two parts of the common atrium (i.e., interatrial flow),
- the septum primum is fenestrated spontaneously in its superior regions by apoptosis to create ***ostium secundum***; these fenestrations appear to create the right to left shunt in the fetal circulation which allows the flow of oxygenated blood coming from the umbilical vein to the other organs of the fetal body; in this way, the superior part of the septum primum will be obliterated; though it will be completed by ***septum secundum***,
- a crescent muscular mass of the ventrocranial common atrial wall originates from the right atrium and grows downward on the right side of the septum primum; this infolding will produce the superior segment of the future interatrial septum; this structure is called ***septum secundum*** and it will cover the main part of the ***ostium secundum***; this muscular ***septum secundum*** develops during the fifth and sixth weeks of gestation,
- so, we see that the future interatrial septum is the result of two merging septa: ***septum primum*** and ***septum secundum***,

- the left venous valve and the septum spurium merge with the right side of the septum secundum,
- meanwhile, the pulmonary veins will be relocated from the right atrium to the dorsal wall of the left atrium,
- the defect in the septum secundum is called ***fossa ovalis*** which is usually compensated by ***septum primum***,
- there is a defect in the borders of septum primum and septum secundum called ***foramen ovale***, an obliquely elongated cleft in the interatrial septum which is open as long as fetal circulation persists; after birth, the transition of circulation from fetal circulation to normal circulation leads to increased pressure in the left cardiac chambers and closure of foramen ovale: at first physiologically and after a while, anatomically,
- ***sinus venosus*** is the part of tissue separating right pulmonary veins from the superior vena cava (SVC) from the posterior and inferior aspects of the free wall of the right atrium; ***coronary sinus septum*** is the part of myocardial tissue separating coronary sinus from the left atrium (Geva et al. 2014).

The communication between the endocardial cushions and the lower edge septum primum is named the foramen primum or the ostium primum. The ostium primum, as a shunt, helps the oxygenated blood to cross from the left to the right atrium. In the next growth, expansions of the lower and higher endocardia cushions develop toward the rim of the septum primum and block the ostium primum.

Genetic factors related to the development of interatrial septum: a set of genetic studies have shown that atrial septal defects and defects in the conduction system are closely related to NKX2.5 Mutations. The other genes that play the main role in heart development are the GATA4 gene. The product of this gene and its interaction with other gene products including TBX5 play an important in cardiac development. Mutations in this gene alter the transcriptional activity of GATA4 and result in Atrial Septal Defect (ASD), Ventricular Septal Defect (VSD), and pulmonary valvular stenosis (Gourdie et al. 1999; Gourdie et al. 2003; Christoffels et al. 2004; Moorman et al. 2005; Tomita-Mitchell et al. 2007; Remme et al. 2009; Moskowitz et al. 2011; Xin et al. 2013; Stefanovic and Christoffels 2015).

Clinical notes:
- ASD is discussed in detail in Chap. 21; however, some of its developmental notes are discussed here in brief
- If the pulling-down process of septum primum and septum secundum are deficient, a type of defect occurs in the interatrial septum known as ASD secundum or ostium secundum ASD (**ASD II**) which is **the most common type of ASD**
- If the ostium primum is not closed by septum primum coming from the underlying AV cushions, primary atrial septal defect (**ASD I**) occurs which is often in combination with varying degrees of abnormalities in AV cushions; namely AVSD which is discussed in Chap. 20—AV Septal Defects
- In a minority of newborns, fetal circulation persists, leading to a clinical status called persistent fetal circulation (PFC) which is discussed in detail in Chap. 3—Cardiac Physiology; however, PFC leads to increased pressure in the right side over the left side which is the main etiology for persistence of foramen ovale; a disease known as "**persistent foramen Ovale: PFO**" which is discussed under the interatrial defects
- The last major type of interatrial defects is called **Sinus venosus atrial septal defect**, which is due to abnormal attachment of venae cavae (often the superior vena cava) leading to atrial septal defect which is usually associated with anomalous attachment of pulmonary veins; this defect is often discussed under anomalous pulmonary venous drainage (Kerut et al. 2001; Sukernik et al. 2001; Oliver et al. 2002; McCarthy et al. 2003; Van Praagh et al. 2003; Sukernik and Bennett-Guerrero 2007; John et al. 2011; Briggs et al. 2012)

Septum development in the atrioventricular canal: creation of the atrioventricular cushions associated with tricuspid and mitral valves.

At the fifth week of gestation, the superior and inferior endocardial cushions are going to be created; so, they gradually appear over the primitive left ventricle. Then, an endocardial mass is produced on the ventral and dorsal parts of atrioventricular (AV) canal, and at the same time, this mass is penetrated by mesenchymal cells. In this way, the AV endocardial cushions are made close to each other; while in the next stage, they merge

together and are separated to form the left and the right AV canals; these AV canals could discriminate incompletely the primordial ventricle from the primordial atrium.

However, specialized parts of extracellular matrix or cardiac jelly play crucial role in development of endocardial cushion; this is why the effect of specific molecules including hyaluronic acid, hyaluronan, fibronectin, fibrillin, proteoglycans, and collagens in cardiac jelly plays a leading role (Lockhart et al. 2011; Ray and Niswander 2012; Lalani and Belmont 2014).

The cells that constitute the endocardial cushion tissues are primarily endocardial in origin; however, these endothelial cells migrate into the inner layers of the heart tube to create the primitive mesodermal tissue of this tube, which is located in the crux of the heart. This critical process in formation of cardiac cushions is called "**endothelial to mesenchymal transition of endothelial cells**" in cardiac cushions (Zhang et al. 2014; Davey and Rychik 2016).

There is a detailed list of cellular and molecular factors which play their role in the development of cardiac cushions and any impairment in their role may lead to endocardial cushion defects; these factors include but are not limited to the following:

- transforming growth factors and proteins (like BMP: bone morphogenetic protein),
- intercellular signaling molecules and enzymes,
- extracellular matrices,
- transcription factors and mutations in their related genes; like GATA4 transcription factor, TGF beta, FOG factor, Smad4, Zic family member 3 (Zic3), NK2 homeobox 5 (Nkx2.5) and T-box protein 5 (Tbx5),
- mutations in genes such as CYSTEINE-RICH PROTEIN WITH EGF-LIKE DOMAINS (CRELD1; a cell adhesion molecule) (Yamagishi et al. 2009; Lockhart et al. 2011; Moskowitz et al. 2011; Ray and Niswander 2012; Garside et al. 2013; Liu et al. 2013; Paffett-Lugassy et al. 2013; Xin et al. 2013; Lalani and Belmont 2014; Kathiriya et al. 2015; Stefanovic and Christoffels 2015; Gordon and Gordon 2016).

Atrioventricular Valves

For creation of the atrioventricular (AV) valves, the following steps happen:

- the AV valves are produced in a process called "**endothelial to mesenchymal transition of endothelial cells**" in cardiac cushions through the following subsequent stages,
- the endocardial cushions are the "progenitors" of the AV valves,
- the embryologic cells that constitute the endocardial cushions are endothelial cells migrating into the inner layer of the heart tube; this migration creates primary mesodermal tissue of the heart tube which is located in the heart crux,
- afterwards, the AV endocardial cushions merge,
- then the mesenchymal tissue proliferates locally and surrounds the orifice of the AV canals,
- in the next stage, the blood follow dips out the tissue on the ventricular surface of the mesenchymal proliferations, which leads to more final form of the valves,
- however, there is still persistence of the *valve links* to the ventricular wall by muscular cords; in the last stage, the muscular cords are changed to a dense connective tissue, followed by obliteration of muscular part of the cords,
- now the valves include connective tissue endorsed by endocardium; which are attached by chordae tendineae to the papillary muscles (Fig. 7),
- and now we have two final valves: the *two leaflet* valve in the left atrioventricular canal which is bicuspid, known as ***mitral valve***; and *three leaflet* valve in the right atrioventricular canal known as ***tricuspid valve*** (Gaussin et al. 2005; Zhang et al. 2014; Davey and Rychik 2016).

Many cellular and molecular factors play their role in normal development of AV cushions; any impairment in their process leads to impaired endocardial cushion development; some of these factors are presented here:

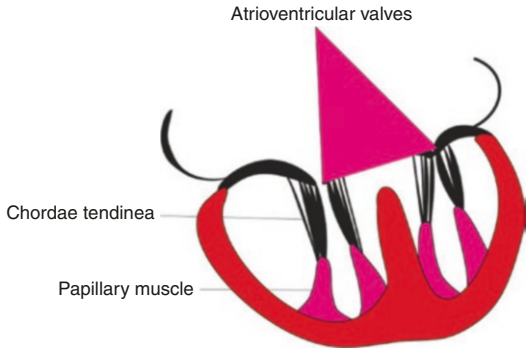

Fig. 7 Development of the atrioventricular valves and chordae tendineae

- transforming growth factors and proteins (like BMP: Bone Morphogenetic Protein),
- intercellular signaling molecules and enzymes,
- transcription factors and mutations in their related genes; like GATA4 transcription factor, TGF beta, FOG factor, Smad4, Zic family member 3 (Zic3), NK2 homeobox 5 (Nkx2.5) and T-box protein 5 (Tbx5),
- extracellular matrices (Yamagishi et al. 2009; Moskowitz et al. 2011; Ray and Niswander 2012; Garside et al. 2013; Liu et al. 2013; Kathiriya et al. 2015; Stefanovic and Christoffels 2015).

Clinical note:
If normal development of the endocardial cushions is impaired, the resulting defects would be seen as *defects in the septum* (at the crux of the heart) and also, impairment in normal development of the AV valves, a clinical state known as atrioventricular septal defect "AVSD." However, these abnormalities in the septum and the AV valves do not have a constant spectrum with varying degrees; so, there are different phenotypes seen in patients with AVSD; detailed discussion on this disease could be found in Chap. 20—AV Septal Defects

Septum development in the ventricles: creation of the interventricular septum (IVS).

At the beginning of fifth week, the primeval ventricles start to expand and create the apical portions of the future ventricles from the primary heart tube. The interventricular septum (IVS) sulcus is the externally separating margin of right and left ventricles; while the internal separator of right and left ventricle is the bulboventricular flange which is part of the primitive ventricle and leads to development of the muscular part of IVS. Development of the primeval ventricles is one of the main steps in development of IVS. There are two main parts in IVS:

- the muscular IVS developed from the bulboventricular flange,
- the membranous IVS connects the upper margin of the bulboventricular flange to the anterior and posterior endocardial cushions.

However, there are a number of following sequential events leading to development of IVS:

- the ***first*** sign of division in primordial ventricle is creation of muscular IVS which is a median ridge in the ventricle floor adjacent to its apex; the edge of muscular IVS is concave and free,
- during early stage of development, IVS achieves its height by expansion of the ventricles on each side,
- afterwards, IVS myoblasts start active proliferation, resulting in increased size,
- the next step is conus septum completion, which happens as a result of tissue extension, starting from the inferior part of endocardial cushion alongside top of the muscular IVS; these parts of tissue finally merge with the neighboring portion of the conus septum,
- and the final step is closure of the opening above the muscular IVS; when the interventricular foramen closes completely, the membranous part of the IVS is formed,
- three sources of tissue take part in the closure of the interventricular opening and formation of the membranous IVS: the *left* bulbar ridge, the *right* bulbar ridge, and the endocardial cushions.

The *primary ventricular septum* or *primary ventricular fold* is produced following the trabeculation of the ventral part of the muscular IVS. However, there is a smooth part on the dorsal wall of IVS, named the ***inlet septum***; this nomenclature is used because it is located nearby the AV canals. The *moderator band* or *septomarginal trabecula* is located on the right wall of muscular IVS, between the primary trabeculated fold and the inlet septum. This structure is a firm connection between the muscular septum and the anterior papillary muscle. When the right ventricular chamber expands, the moderator band is formed nearby the AV canal and dorsal muscular IVS. Eventually, a large part of the mature right ventricular chamber is formed by this expansion. However, if this anatomic area expands incompletely, the developing tricuspid part of the atrioventricular canal remains attached to the interventricular foramen, leading to tricuspid atresia and/or other tricuspid valve anomalies (Lamers and Moorman 2002; Gittenberger-de Groot et al. 2005; Togi et al. 2006; Lin et al. 2012; Poelmann et al. 2014).

Failure or gaps in the development of IVS lead to different forms of VSD; a detailed discussion on VSD is provided in Chap. 21.

Septum Development in the Truncus Arteriosus and Conus Cordis

There is a paired ridge, composed of two cushions, which appears in opposing sites of the truncus. These two ridges are located as follows:

- on the **right side** of superior wall: the right swelling lies on the superior truncus,
- on the **left side** of the inferior wall: the left swelling lies on the inferior truncus.

During the fourth week of gestation, ***the right-sided swelling*** located on superior site of truncus progresses distally and towards the left. Meanwhile, ***the left-sided swelling*** located on inferior truncus develops distally to the right. Henceforward, these swellings grow toward the aortic arch, while at the same time, they turn around each other. During this turning movement, they foreshadow the spiral pathway of the upcoming septum (Webb et al. 2003; Anderson et al. 2010).

These swellings deal with a spiral twist of about 180 degrees. Some of the neural crest cells are transferred from the embryonic pharynx and pharyngeal arches to arrive in these edges. The streaming of blood from the ventricles is one of the main factors that may play a major role in the spiral orientation of the bulbar and truncal edges (Webb et al. 2003; Anderson et al. 2012).

Anyway, this model of development results in the formation of a spiral *aorticopulmonary septum* when the edges merge. However, after these edges are completely merged, they make the *aorticopulmonary septum*, separating the truncus into two parts: an ***aortic channel*** and a ***pulmonary channel*** (Fig. 8) (Steding and Seidl 1981; Webb et al. 2003; Okamoto et al. 2010).

During the fifth week of gestation, ridges from the subendocardial tissue are formed in the **common outflow tract**. The spiral orientation of these ridges results in a spiral *aorticopulmonary septum* during fusion of these ridges. This is the septum that divides the outflow tract into two channels, the pulmonary trunk and the aorta. The second heart field

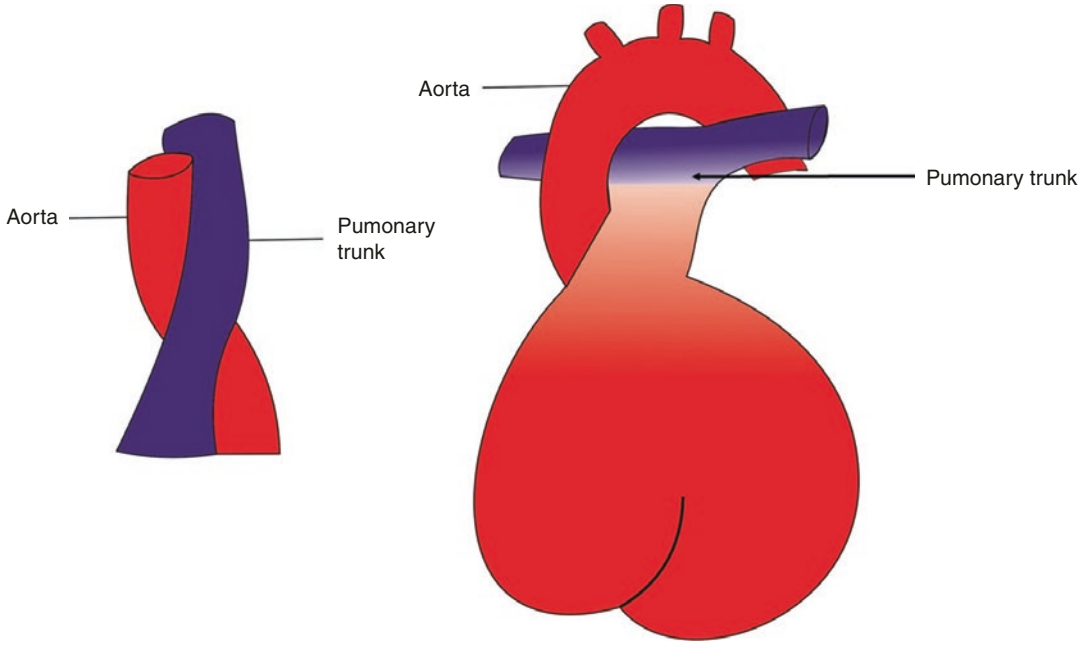

Fig. 8 Septation of the heart outflow tract and complete the ventricular separation. Formation of the conotruncal ridge; Conotruncal ridge fuses with the others compartment to complete the interventricular septum

(SHF) plays a crucial role in the development of the outflow tract. Any impairment in SHF or neural crest results in major defects in growth and development of the conotruncal region (Steding and Seidl 1981; Webb et al. 2003; Restivo et al. 2006).

Semilunar Valves Formation

When conotruncal septa are formed, two other cushions are developed which oppose each other in the outflow tract; they are called "the intercalated cushion in the distal conal fragment"; the new cushions, after being remodeled, make two main ***outflow tract*** cushions. These two cushions together with the lateral intercalated cushions are excavated; the final result of this process is creating cavities at the origin of the future pulmonary artery and ascending aorta. The primordial deviations from these cavities and the intervening tissues are *valvular sinuses* and *semilunar valves*. A set of studies in mice show that semilunar valve leaflets originate mainly from endocardial cushion tissue,

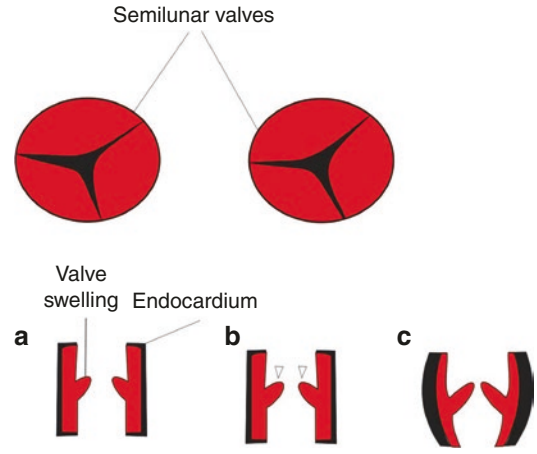

Fig. 9 Development of semilunar valves at weeks 6 (**a**), 7 (**b**), and 9 (**c**). The superior surface is hollowed to form the valves

associated somewhat with neural crest cells and epicardial cells. The development of semilunar valves in human is completed up to ninth week (Fig. 9) (Anderson et al. 2003b; Hinton and Yutzey 2011; Goenezen et al. 2012; Lin et al. 2012; Sherif 2014; van Geemen et al. 2016).

Development of the Cardiac Conducting System in the Heart

The Cardiac Conducting System (CCS) is composed of several integral components in a delicate hierarchy which is the mainstay for effective mechanical contractions of the heart chambers (Desplantez et al. 2007; Dun and Boyden 2008; Atkinson et al. 2011).

- the sinoatrial (SA) node which is the main ***excitatory and impulse generating*** location in the heart, generating the regular and rhythmic leading impulses of the heart; they have the most rapid intrinsic rate for impulse generation all over the cardiac cells,
- specialized conduction system known as "***conductive cells***" which is mainly composed of the atrioventricular conduction pathways, atrioventricular (AV) node, the His bundle and its right and left branches; finally, there are the Purkinje fiber cells or the Purkinje fiber network which is distributed over all parts of the ventricles and conduct the electrical impulse effectively and rapidly over the ventricles (Fig. 10).

Development of the sinoatrial (SA) node: during the very early phases of heart development, while there is no conduction system development, all of the epithelioid myocytes are electrically active; however, more sophisticated studies have shown that pacemaking area cells have been evolved as a primitive area in the primary sinus venosus and atrium well before heart begins; these cells are developed and start signaling towards the outflow tract of the developing heart well before any other part of the CCS is developed; their impulses are spread over the heart through gap junctions and connexin proteins (Jalife et al. 1999; Mikawa and Hurtado 2007).

The pacemaker cells changing later to SA node are placed in the caudal portion of the left heart tube at the beginning of their development. At first, the primitive atrium plays the main role of pacemaker in the heart, but in the next phases of development, this role is transferred to sinus venosus. Later, during the fourth week, SA node develops. It is located in the right wall of the sinus venous during early phases of development; however, in the next couple of weeks, its gradual development leads to its merge with the right atrial wall. In the normal heart, SA node lies in the cephalic portion of the posterior wall of right atrium just near the orifice of SVC. During its normal function, SA node has a complex architecture leading to heterogeneous electrical activity. Also, pacemaking cells, especially in SA node, have a number of specific specifications:

- higher rate of spontaneous beating,
- faster activation of the funny current (I_f),
- greater density of the funny current (Mikawa and Hurtado 2007).

Development of AV node: during the next phases of CCS development, the cells derived from left wall of sinus venous, form the atrioventricular node and bundle; these cells are usually placed in the inferior part of interatrial septum and anterior to the coronary sinus foramen. The AV node lies just superior to the endocardial cushions. Development of AV node is a multiple step mechanism. The first theory is that AV node cells are in fact a subpopulation of the primary myocardial cells which their differentiation into "normal" mature myocardial cells is restrained, leading to AV node cells with slow conducive properties; however, additional cellular and molecular theories (including signaling mechanism) are proposed for AV node development; these are beyond the scope of this chapter (Christoffels et al. 2004; Moorman et al. 2005; Mikawa and Hurtado 2007).

During the development of AV node, there are three basic changes in differentiation of the impulse propagation pattern of the CCS; these changes occur during looping of the heart tube and ensure productive and successful pumping of blood in the four-chambered heart; they are mainly the result of the following three major developmental steps:

1. **significant slowdown of impulse velocity at the AV junction**: this impulse slowdown is synchronized with morphologic cleavage between atrial and ventricular chambers; also,

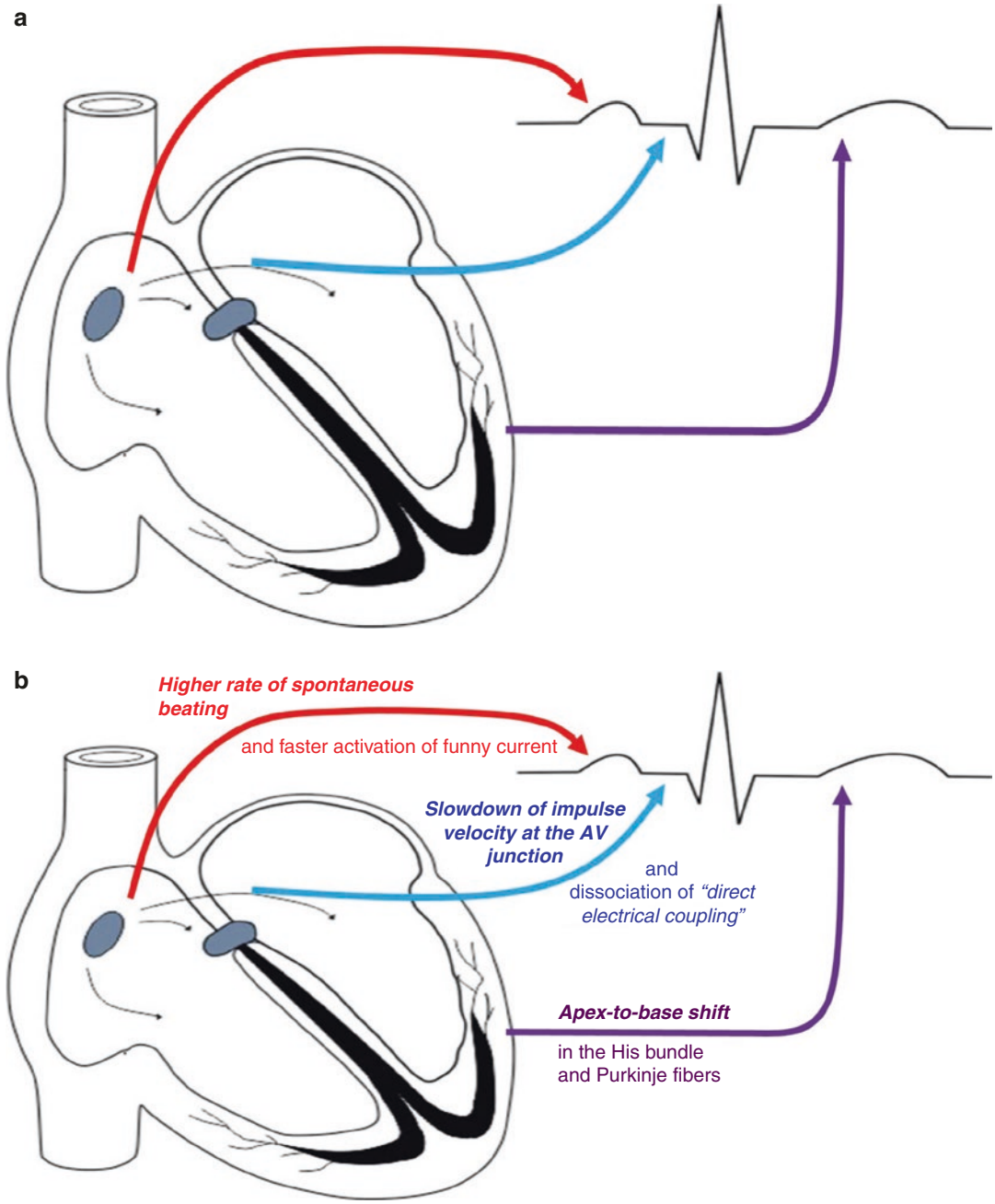

Fig. 10 Cardiac conductive system and its elements; in left, see the relationship of normal electrocardiography with the elements of the system. (**a**) relationship of each anatomical segment with electrocardiograph; (**b**) the embryologic "role definition" for each of the electrical segments of the heart during its development. (Modified from Dabbagh A. "Cardiac physiology"; In "Postoperative Critical Care for Cardiac Surgical Patients." Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp. 1–39. Published with kind permission of © Springer, 2014. All Rights Reserved)

this time delay in combination with development of AV cushions leads to production of an effective peristaltic wave in myocardial contraction; the final result will be augmented pumping efficiency of the developing heart,
2. the second step is **dissociation of "*direct electrical coupling*"** between atrial syncytium and ventricular syncytium due to creation of the interventricular septum,
3. **shift in the electrical direction of the impulse**: when septation occurs in the ventricular chambers, there is a very clear and specific change in the process of impulse generation and propagation and that is a dramatic shift in the electrical direction of the impulse from "*base-to-apex*" model to "*apex-to-base*" model (Mikawa and Hurtado 2007).

Development of bundle branches and His bundles: during the next developmental phases, the AV node bundle fibers pass throw the atrium to the ventricles and divide into the right and left bundle branches, distributing over the ventricular myocardial tissue. The growth of the AV node is simultaneous with the formation of the bundle of His, a specialized conducting fiber, connecting the bundle branches to the Purkinje fibers in the peripheral ventricular conduction system. His bundles distribute into the left and the right ventricles by the moderator band.

Development of Purkinje fibers: development of the Purkinje fibers is from the "working myocytes" as a result of interactions between contractile myocytes with endocardial cells and arterial cells, leading to development of ***subendocardial*** and ***intra-myocardial*** Purkinje cells, respectively; also, coronary arteries have a very essential role in differentiation of Purkinje cells; endothelin signaling is another main factor that promotes transdifferentiation process of the Purkinje fiber (Gourdie et al. 1999; Gourdie et al. 2003; Gassanov et al. 2004; Mikawa and Hurtado 2007; Hua et al. 2014).

The CCS has a pivotal role in the function of the heart; any developmental defects leading to abnormalities in the CCS lead to life-threatening cardiac arrhythmias (Wu et al. 2014). Also, the repair of congenital heart defects, especially in patients with ventricular septal defects, is associated with a great risk of damage during surgical correction in all of these conducting structures (Racker 2004).

Atrioventricular (AV) Valve Anomalies

Abnormalities in AV valve development significantly contribute to errors in the remodeling process that leads to formation of valve leaflets, chordae tendineae, and papillary muscles; they originate from endocardial cushion and ventricular myocardium. Partitioning of truncus arteriosus and conus arteriosus in the fifth week of embryologic development are associated with the spiral development and twisting migration of neural crest cells; the final result as mentioned before is the development of the structures known later as "outflow tracts" and "great arteries" (Anderson et al. 2003b; Restivo et al. 2006).

In the ***pulmonary tract*** system, the related conus known as *pulmonary conus* takes part in the formation of the infundibulum which is the anatomic structure between pulmonary valve and the AV valves on one side and the muscular infundibulum on the other side. In ***outflow tract*** of the systemic circulation, the subaortic conus is obliterated leading to development of the aortic valve surrounded by fibrous continuity of the AV valves (Hinton and Yutzey 2011).

Till now, the main pathogenesis mechanism of AV valve atresia (leading to complete obliteration of the orifice of each valve) is not well known. When the AV septum is not formed, the wedging and remodeling of valves are impaired and consequently, alignment of the AV canals with their appropriate ventricles fails. It seems to be the underlying mechanism leading to single inlet for the ventricle: ventricular inflow from both atria.

Likewise, in "**DORV: double-outlet right ventricle,**" there may be double outlets for a ven-

tricle, due to malalignment of the outflow tract; in other words, the affected ventricle has both the aorta and the pulmonary artery. In this disease, the aortic and pulmonary outflow tracts link to the right ventricle, associated in almost all cases with a ventricular septal defect; leading to arterial blood flow leaving the right ventricle, while the blood is a mixture of high oxygenated and poor oxygenated blood. In these patients, the ductus arteriosus links the pulmonary trunk and aorta to each other. Impairment in biventricular circulation leading to a univentricular heart function leads to left ventricle driven circulation, enlargement of the left ventricle and hypoplastic right ventricle; ductus arteriosus should remain open. Usually, this condition leads to cardiac failure unless treated. This disease is discussed more in Chap. 30—Double Outlet Right Ventricle (Anderson et al. 2001; Anderson et al. 2003b; Mahle et al. 2008).

Stenosis of Cardiac Semilunar Valves

Stenosis of the semilunar valve is defined as stenosis of either the aortic valve or the pulmonary valve. These conditions are discussed in Chap. 24—Congenital Aortic Valve Anomalies. Congenital valvular stenosis is due to abnormal cavitation and remodeling within the distal conal cushion tissue responsible for forming the aortic semilunar valves, leading to different congenital diseases of the aortic valve.

Cardiac Outflow Tract Septation Anomalies

Truncus arteriosus: cardiac neural crest cells are multipotent migratory cells that contribute to the cardiac outflow tract formation and the pharyngeal arch arteries. Today we know that a great number of many of the outflow tract septation malformations are in association with abnormal development of neural crest cells; as a result, the conotruncal septa do not form at all, leading to **persistent truncus arteriosus**. This abnormality will inevitably embrace a defect in ventricular septation, leading to mixing of blood during departure from two ventricles; that is, in the common outflow tract; however, the result of this mixing is mainly a left-to-right shunt leading to pulmonary hypertension (Fig. 11). If not treated, the child usually dies within the first 2 years of life. This defect is usually corrected surgically, by fixing the VSD and implanting a valved prosthetic shunt connecting the right ventricle and the pulmonary arteries.

Transposition of the great vessels: in about 5 per 10,000 live-born infants, the conotruncal septa develop but without the usual spiral pattern, leading to transposition of the great vessels, in which the left ventricle empties into the pulmonary circulation and the right ventricle empties into the systemic circulation. Inversion of the great vessels is often fatal unless the ductus arteriosus remains patent or is accompanied by intrinsic ASD or VSD or by surgically introduced atrial defects aiming to establish an interatrial communication and hence, allowing the deoxygenated systemic and the newly oxygenated pulmonary blood to mix. Inversion can be surgically modified with a favorable prognosis. Nevertheless, it is the main cause of death in infants with cyanotic heart disease younger than 1 year old. A full discussion of the disease is presented in Chap. 21—Transposition of Great Vessels.

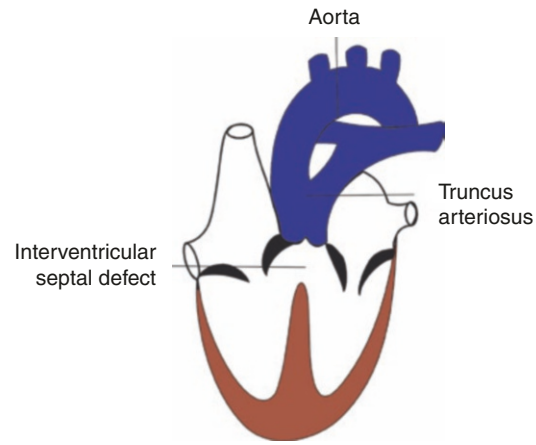

Fig. 11 The outflow cardiac tract septation defects

Tetralogy of Fallot (TOF): TOF is a syndrome described by Danish Niels Stensonin 1671, then reported by Edouard Sandifort in 1777, and the exact anatomy of TOF illustrated by William Hunter from St Georges Hospital Medical School, London in 1784. It was in 1888 that Etienne-Louis Arthur Fallot described L'anatomie pathologique de la maladie bleu; in 1924, the term "tetralogy of Fallot" was created for the first time by Canadian Maude Abbott (Berry 2006; Evans 2008; Van Praagh 2009). The term ***tetralogy*** refers to four classic malformations, demonstrated as a graphic in Fig. 12 and includes:

- pulmonary stenosis,
- ventricular septal defect,
- rightward displacement of the aorta (usually known as overriding of aorta),
- right ventricular hypertrophy.

The main etiologic mechanism is uneven separation of the outflow tract which results to overriding of aorta and also, malalignment of the muscular outlet septum regarding right and left ventricles; these defects lead to increased filling pressures in the right ventricle, with resultant right ventricular hypertrophy. TOF is among the common cyanotic congenital heart diseases and is generally corrected surgically, including release of the pulmonary trunk obstruction, repair of ventricular septal defect and at the same time, correction of overriding; a few years later a considerable number of patients refer for correction of the pulmonary insufficiency which is a sequel of pulmonary stenosis repair. TOF is presented in detail in Chap. 21 (Therrien et al. 2005; Apitz et al. 2009; Starr 2010).

Vascular Formation

Two main mechanisms are involved in development of blood vessels:

1. **vasculogenesis**: a process producing vessels through the process of angioblast coalescence; this mechanism is responsible for production of the two main vessels, the dorsal aorta and cardinal veins (Williams et al. 2010; Charpentier et al. 2015),
2. **angiogenesis**: new buds emerge from the preexisting vessels and in this way, new vessels are created; this is the mechanism responsible for development of all body vessels except for dorsal aorta and cardinal veins; however, vascular endothelial growth factor (VEGF) and other growth factors play a crucial role throughout this mechanism (Charpentier and Conlon 2014).

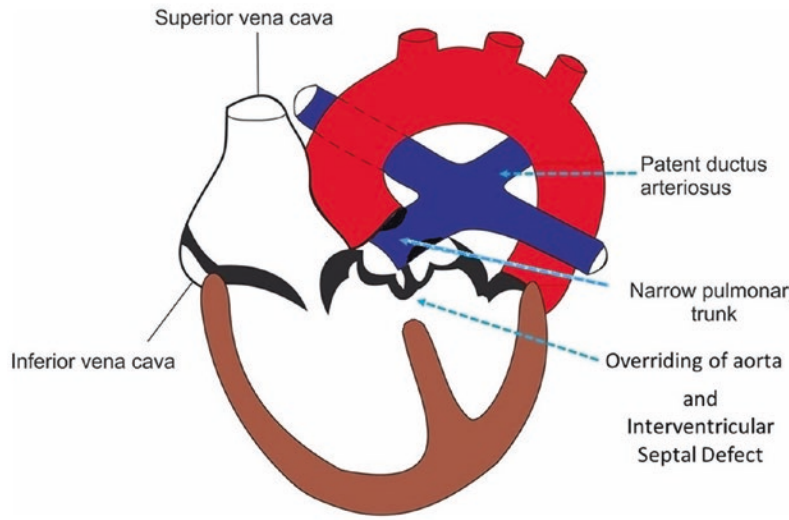

Fig. 12 Tetralogy of Fallotincluding pulmonary stenosis, overriding of the aorta, interventricular septal defect, and hypertrophy of the right ventricle

Arterial System

Development of Aortic Arches

The ***aortic arches*** are a series of paired developing vascular organs in the embryological development; in addition, they are also known as ***pharyngeal arch arteries*** or ***branchial arches*** and they give origin to a number of important vascular structures.

Creation of aortic arches begins between 22nd to 24th days of development. At first a pair arches are formed; then, following the folding of body, the endocardial tubes move towards the future thorax; meanwhile, the cranial ends of the attached aortae are drawn into a dorsoventral loop. This leads to location of the first aortic arch pair into the condensed mesenchyme of the first pharyngeal arches in each side of the developing pharynx.

The arterial lumen of the aortic arch arises from the ventral part of the aortic sac, which is an enlargement at the cranial part of the truncus arteriosus. They are linked to the right and left dorsal aortae. Aortic arches are located ventral to the dorsal aorta. The dorsal aortae persist as discrete vessels in the aortic arches area; however, in the fourth week of gestation, they merge together throughout the fourth thoracic segment to the fourth lumbar segment to make a dorsal aorta in midline. Development of aorta occurs during the third week of development, in relation with development of the endocardial tube. During days 26 to 29, through the process of angiogenesis and vasculogenesis, the second, third, fourth, and sixth arches grow inside their related pharyngeal arches; then, they are incorporated with EPCs that are transferred from the inclosing mesoderm. Also, neural crest mesenchymal cells in the pharyngeal arches play a main role in the usual growth of the arch arteries; here the neural crest cells do not have a direct relationship to the endothelium of these vessels (Kau et al. 2007).

Development of Arterial Tree from Aortic Arches

During 28th to 32nd days of embryonic development, blood departs the heart via the outflow tract and comes back to the heart through the extrapericardial aortic sac. There is a very important connection between the **aortic sac** and **bilateral dorsal aortae**; this connection is developed through third, fourth, and sixth pharyngeal arch arteries, which run in their corresponding pharyngeal arches and then, separate in the dorsal region; finally, they merge with the paired dorsal aortae. Later, during the course of development, the **aortic sac** obliterates and is no more recognized (days 37–42). A summary of the organs created during the embryologic period form the aortic arches are discussed here **for each aortic arch** based on related extensive studies; also, a very brief summary is presented in Table 1 (Graham 2003; Kau et al. 2007; Strilic et al. 2009; Kellenberger 2010; Mirilas 2011; Lammert

Table 1 Embryologic aortic arch pairs (Kau et al. 2007; Rana et al. 2014)

Aortic arch pair	Originated arteries
1st pair	Maxillary and external carotid arteries
2nd pair	Stapedial arteries
3rd pair (carotid arch)	Internal carotid artery also, proximal parts of the third pair constitute the common carotid arteries
4th pair	***Right arch***: Constitutes the proximal right subclavian artery until the origin of right internal mammary branch ***Left arch***: Originates the aortic arch between left common carotid artery and left subclavian artery (ductus arteriosus)
5th pair	Rudimentary vessels
6th pair	***Right arch***: Constitutes the right pulmonary artery ***Left arch***: The main and left pulmonary artery and ductus arteriosus
7th pairs	***Right arch***: Constitutes part of the right subclavian artery; in addition, the right fourth arch and the right dorsal aorta contribute information of the right subclavian artery ***Left arch***: The left subclavian artery

and Axnick 2012; Stojanovska et al. 2012; Bamforth et al. 2013; Neufeld et al. 2014; Rana et al. 2014; Gupta et al. 2015; Menshawi et al. 2015; Plein et al. 2015; Gupta et al. 2016).

The first aortic arches: as the future arches are going to be formed, the first two arches go to remission and go to their earlier states. Later, as the second arch develops, the first arch degenerates absolutely (except a small remnant which makes a part of the maxillary arteries).

The second aortic arches: by day 26th, the second aortic arch grows in the second pharyngeal arches and joins the dorsal aortae to the aortic sac; however, the second arch degenerates at the time that the sixth arch is developed; just a small part of the second arch remains which makes the stapedial artery, providing future blood supply to the stapes bone in the developing ear.

The third and fourth aortic arches: during regression of the first arch on day 25, the third and fourth aortic arches are formed; the aortic arch is made of the joint venture of left fourth aortic arch with the merged dorsal aorta and a small part of the aortic sac; this combination is converted to ***ascending aorta*** or to ***aortic arch*** and ***the most cranial part of the descending aorta***. When the dorsal aortic segments are merged, they lead to caudal parts of the descending aorta at the fourth thoracic level.

During these developmental processes, the fourth arch is much more profuse and protuberant than the third and sixth arterial arches.

The **third aortic arch** is attached to the dorsal aortae at its cranial part; this attachment has an "end-to-side" fashion, leading to development of ***internal carotid arteries*** as cranial extensions of this attachment.

There is another part of dorsal aorta located between the third and the fourth aortic arches; known as "***carotid duct***"; this arterial segment is narrower than caudal segments of dorsal aorta.

In the next stage of arterial system development, the dorsal aorta disappear on either side by day 35; these aortic parts join the third and the fourth arch arteries. Therefore, the third aortic arches drains totally into the cranial parts of the dorsal aortae; which perfuses the head.

The arteries derived from the third arch include:

- right common carotid artery,
- left common carotid artery,
- proximal part of the right and left internal carotid arteries.

The distal part of each **internal carotid artery** is developed from the cranial part of the ipsilateral dorsal aorta, and the right and left external carotid arteries develop from the common carotids.

The fifth aortic arches: the fifth pair is **not** involved in these developmental stages; as a matter of fact, some authors have even questioned its presence or at least, claimed that no specific role is attributable to this arch in development of congenital heart diseases; however, others have defined some role (Bamforth et al. 2013; Gupta et al. 2015; Gupta et al. 2016).

The sixth aortic arches: it is formed on day 29, while the second arch degenerates simultaneously; the proximal end of the aortic sac gives rise to the right and left sixth arches which are asymmetrical in the next developmental phases. The right sixth arch loses its distal connection with the right dorsal aorta by the end of eighth week; in comparison, the left sixth arch does not disappear and its distal part forms the ***ductus arteriosus***. This duct lets the blood transfer from the pulmonary trunk into the descending aorta during gestation. After birth, this duct is closed and is transformed later to ligamentum arteriosum, a rudimentary joint between pulmonary trunk and aorta.

The uneven growth of the right and left sixth arches has another consequence: ***asymmetry*** *between left and right recurrent laryngeal nerves*; which are branches of the vagus nerves. The laryngeal nerves rise initially under the level of the sixth arch; then, they pass under the right and left sixth arches. Recurrent laryngeal nerves innervate intrinsic muscles of the laryngeal system. Throughout development, the larynx moves cranially in relation to aortic arch; however, left recurrent laryngeal nerve is trapped below the

left sixth arch and remains circled under the developing ligamentum arteriosum. In contrast to the left recurrent nerve, the right recurrent laryngeal nerve is entrapped below the fourth arch which is changed later to the right subclavian artery due to degeneration of the distal portion of the right sixth aortic arch and also no further development in the fifth arch.

Finally, during these phases, ***sprouts of pulmonary trunk*** emerge as the following order: sprouts of the pulmonary trunk could be visible at the caudal segment of the sixth aortic arch. The embryonic pulmonary arteries grow in the splanchnopleuric mesoderm; they initially join the fourth aortic arch; then, they create a new and secondary link with the sixth arch before missing their link with the fourth aortic arches. In fact, the pulmonary arteries join the sixth arch arteries and in the next stages, to the pulmonary trunk; however, pulmonary artery buds are not near each other in this stage; instead, the lumen of the aortic sac is insinuated between them; at this time, the right primary pulmonary artery is more laterally located compared to the left primary pulmonary artery. The distal part of the pulmonary arteries in the lung tissue anastomoses with the existing vasculature in the mesenchymal tissue surrounding the bronchial sprouts.

The seventh aortic arches: the seventh pair of dorsal intersegmental aortae meet and join; left and right ***subclavian arteries*** originate at the caudal point of their convergence; then, they vegetate towards the sprouts of the corresponding upper limb. The ***right subclavian*** artery which will supply the upper limbs has a triple-based origin:

1. the right seventh intersegmental artery,
2. a short segment of the right dorsal aorta,
3. the right fourth arch.

The brachiocephalic arteries are derived by the modification of the joint area of the aortic sac and the right fourth arch. The ***left subclavian artery*** provides blood to left upper limb; it is developed progressively from the ascending aorta (Menshawi et al. 2015).

By the seventh week, the right dorsal aorta is disconnected from the merged "right 6th arch and midline dorsal aorta"; however, preserving its connection to the right fourth arch. In addition, the right dorsal aorta obtains a branch named the right seventh cervical intersegmental artery, which grows into the right upper limb sprout area.

Also, at the dorsal aspect of the dorsal aortae, a number of small intersegmental arteries sprout at regular distances; they run towards the developing spinal cord to support blood supply to the future spinal cord (Fig. 13).

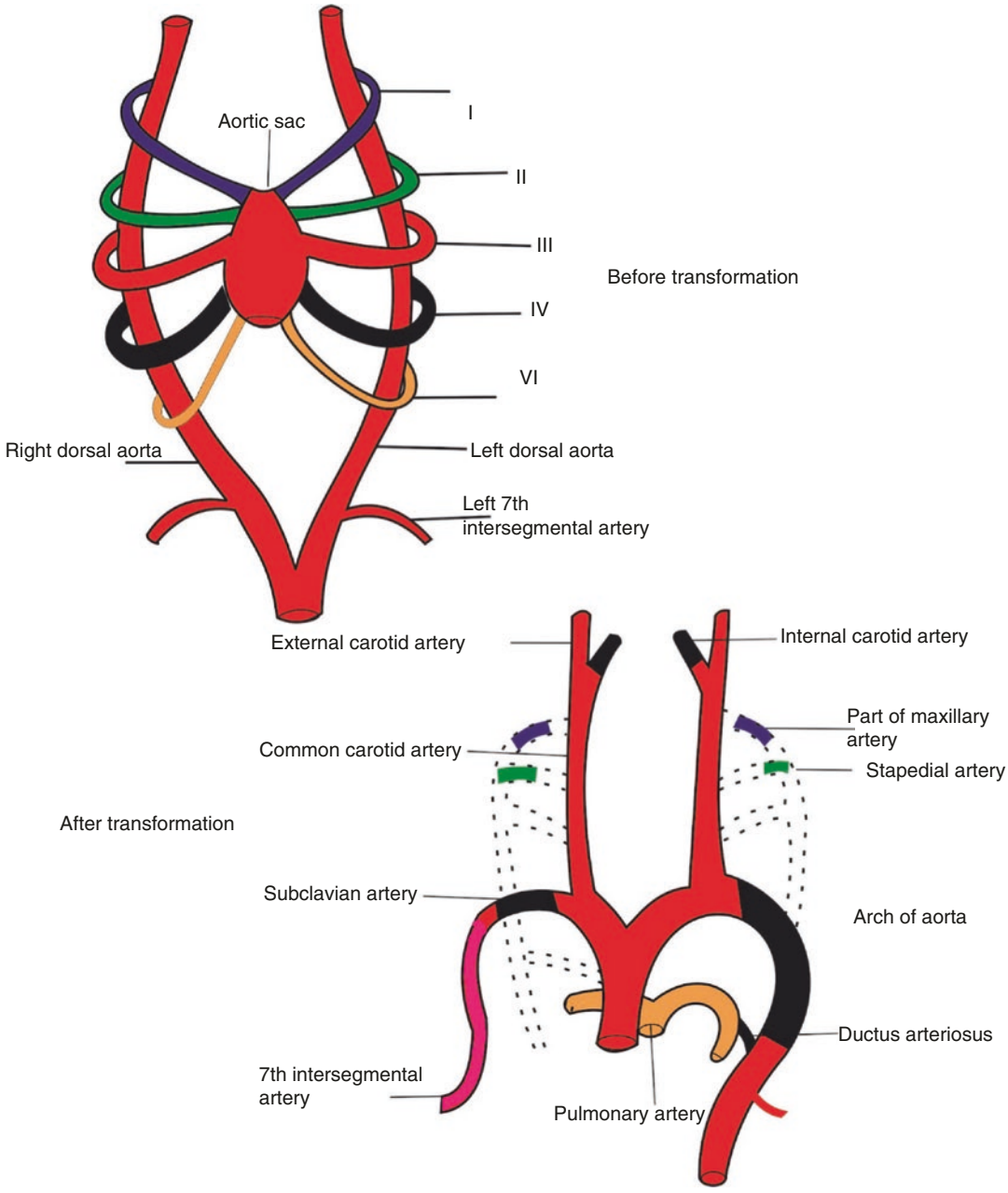

Fig. 13 Schematic drawings of the aortic arches and dorsal aorta before transformation into the definitive vascular pattern and after transformation

Fate of the Vitelline and Umbilical Arteries

The umbilical vesicle (yolk sac), allantois, and chorion are supplied by the unpaired ventral branches of the dorsal aorta. The 3 vitelline arteries perfuse the embryologic segments as they pass to the vesicle and later the primitive gut by the following order:

Celiac arterial trunk is the most superior of the three abdominal vitelline arteries and supplies the **foregut**. During its course, celiac trunk initially joins the dorsal aorta at the seventh cervical level; later, this connection continues down to the 12th thoracic level. The branches of celiac artery vascularize the abdominal part of the foregut, the abdominal esophagus up to the descending segment of the duodenum, and also liver, pancreas, gallbladder and spleen. The branch perfusing spleen develops within the mesoderm of the dorsal mesogastrium. Dorsal mesogastrium is the portion of the dorsal mesentery that suspends the stomach (Cavdar et al. 1997; Yi et al. 2008; Stimec et al. 2011).

Superior mesenteric artery (SMA) is the second abdominal vitelline artery which supplies the **midgut**. At the beginning of its course, SMA joins the dorsal aorta at the second thoracic level. This connection moves later to the first lumbar level. This artery supplies the developing midgut, including *part of intestine extending from descending segment of the duodenum to transverse colon near the left colic flexure* (Rouwet et al. 2000; Bhatnagar et al. 2013).

Inferior mesenteric artery (IMA) is the third and final segment of abdominal vitelline artery which supplies the **hindgut**. IMA initially joins the dorsal aorta at the 12th thoracic level and later ends at the third lumbar level supplying *distal portion of transverse colon, descending colon, sigmoid colon, and the superior rectum* (Moonen et al. 2012; Bhatnagar et al. 2013).

Blood supply to the inferior end of the anorectal canal comes from the branches of the iliac arteries. Two umbilical arteries pass from the connecting stalk (primordial umbilical cord) and locate along sides with vessels in the chorion, the embryonic part of the placenta. The umbilical arteries carry poorly oxygenated blood to the placenta. Proximal parts of the umbilical arteries form the *internal iliac* and *superior vesical* arteries. However, after birth, distal parts of umbilical artery obliterate and become the medial umbilical ligaments.

Dorsal Aorta Give Rise Lateral Branches

Lateral branches of the descending aorta supply the suprarenal glands, gonads, and kidneys. However, these three organs and their arteries have different developmental pathway.

The ***suprarenal glands*** origin in the posterior body wall between the sixth and 12th thoracic segments and supply by a pair of lateral aortic branches that arise at an upper lumbar level. Also, some branches from the renal artery and inferior phrenic artery supply the suprarenal glands, but the suprarenal arteries developing from these aortic branches remain the major supply to the glands (Dutta 2010; Sato 2013).

The presumptive gonads become vascularized by **gonadal arteries** which arise initially at the tenth thoracic level. The gonads descend during development, but the origin of the gonadal arteries becomes stable at the third or fourth lumbar segments. The gonadal arteries elongate, as the gonads (especially the testes) descend further; there are many retroperitoneal anastomoses of the gonadal veins in fetal period and afterwards, left side anastomoses are much more common in both sexes (Raz 2004; Szpinda et al. 2005; Hen et al. 2014; Alfahad and Scott 2015).

In contrast, **the definitive kidneys**, arise in the sacral region and move upward to a lumbar position just below the suprarenal glands. As they migrate, they are vascularized by a sequence of transient aortic side streams that originate at higher levels. These arteries do not elongate for following the ascending kidneys; in contrast, they degenerate. The definitive renal arteries develop from final pair of arteries in the upper lumbar region. Sometime, a more inferior pair of renal arteries remains as accessory renal arteries (Alfahad and Scott 2015).

Intersegmental Branches

At the beginning of the fourth week, the vasculogenesis process leads to raise of small sprouts in the posterolateral segments; these primitive sprouts are located alongside the cervical somites extending through to the sacral somites; they grow up and at the same time, join to dorsal aorta. In **lumbar** and **thoracic** segments, the dorsal branch derived from each of these intersegmental vessels, vascularizes towards the growing neural tube and also, the epimeres (i.e., the dorsal portion of each somite which gives origin to dorsal muscles that are innervated from the related spinal somite). In addition, the dorsal skin is supplied by the cutaneous branches of these arteries (Gans and Northcutt 1983; Northcutt and Gans 1983; Technau and Scholz 2003).

Besides, these intersegmental vessels vascularize the hypomeres; that is, hypomeric muscles and related skin are supplied by the ventral branches of intersegmental vessel (hypomeric muscles are those muscles derived from a hypomere and are also, innervated by an anterior ramus of the related spinal nerve; also, hypomere is the lateral plate of mesoderm which grows up to form the ventral body parts) (Finnegan 1961a, 1961b; Technau and Scholz 2003).

The *ventral intersegmental arteries* in the **thoracic** segments are transformed to intercostal arteries and cutaneous branches; while in the **sacral** and **lumbar** regions, they are developed to lateral sacral and lumbar arteries.

A small branch, the median sacral artery, arises from the dorsal aorta in area of common iliac arteries bifurcation.

In **cervical** regions, the branches derived from intersegmental arteries link together and create a new complex form of vascularization. Some paired vertebral arteries rise from longitudinal branches that anastomose together in order to form a longitudinal vessel, while in back, they secondarily miss their intersegmental links to the aorta. The anastomoses of intersegmental arteries cause to development of some arteries such as ascending cervical, the deep cervical, internal thoracic, superior intercostal, and inferior and superior epigastric arteries (Adameyko and Fried 2016).

Formation of Limb Arteries

During the development of the limb buds, the arteries derived from seven cervical and five lumbar intersegmental arteries grow into the limb buds to provide blood to them; this primitive perfusion system works through an axial artery; which develops alongside the central axis of each limb. In the upper limb, the axial artery gives origin to the following arteries:

- brachial artery,
- anterior interosseous artery of the forearm,
- deep palmar arch of hand,
- radial, ulnar and median arteries.

In the lower limb, in contrast to the upper limb, the axial artery degenerates; so, the external arteries supply the blood flow of the lower limb, finally leading to these main arteries (Funke and Kuhn 1998):

- the small sciatic artery,
- which provides the bloods for the sciatic nerve in the posterior thigh;
- a branch of the popliteal artery,
- a segment of the peroneal artery in the foreleg,
- all additional arteries of the lower limb are derived from the external iliac artery.

The Formation of Coronary Arteries

Coronary arteries originate from two different segments:

1. the proepicardial cells,
2. the epicardial cells.

Vascular development in the myocardial tissue follows the initial development of cardiac loop. The primary coronary beds are formed in the trabeculations of the myocardial tissue; while the underling myocardial cells lead to some degrees of epicardial cell change in the form of “epithelial to mesenchymal transition”; in such a way that the newly formed mesenchymal cells pene-

trate the *endothelial* and *smooth muscle* cells located in the walls of coronary arteries The endothelial plexus located in the sub-epicardial layer, is connected to the endothelial sprouts which are located in the walls of the aortic sinuses;.

On the other hand, the neural crest cells help smooth muscle cells alongside the proximal division of coronary arteries. The endothelial sprouts of coronary arteries develop some forms of vascular ring which is peritruncal; then, they penetrate and merge into the aortic wall. In fact, coronary arteries attach to the aorta following development of endothelial cells; in such a way that coronary arteries penetrate into the aorta. However, there are only two sprouts of coronary arteries which can produce their lumen and orifices: these are the left and the right coronary arteries. This is one of the main differences between coronary arteries and cardiac veins: coronary arteries are perfused from the systemic circulation through the root of aorta; however, coronary sinuses are the specific site for cardiac veins to connect general circulation. Coronary arteries are perfuse about the third trimester. Deals in detail with Coronary Artery Anomalies (Song et al. 2015; Perez-Pomares et al. 2016).

The Formation of Venous System

During the early of second month, three main veins can be found in each side of the body: vitelline vein, umbilical vein and cardinal vein; these veins are discussed here (Fig. 14).

1. **Vitelline veins** or omphalomesenteric veins transfer blood from yolk sac to the sinus venosus. The vitelline veins make a plexus around the duodenal part of the small intestine; afterwards, they arrive in sinus venosus after crossing septum transversum. After trespassing the septum transversum, they are invaded by the liver cords growing into the septum; this will lead to interruption of venous courses. In the final stage, hepatic sinusoids are formed as a

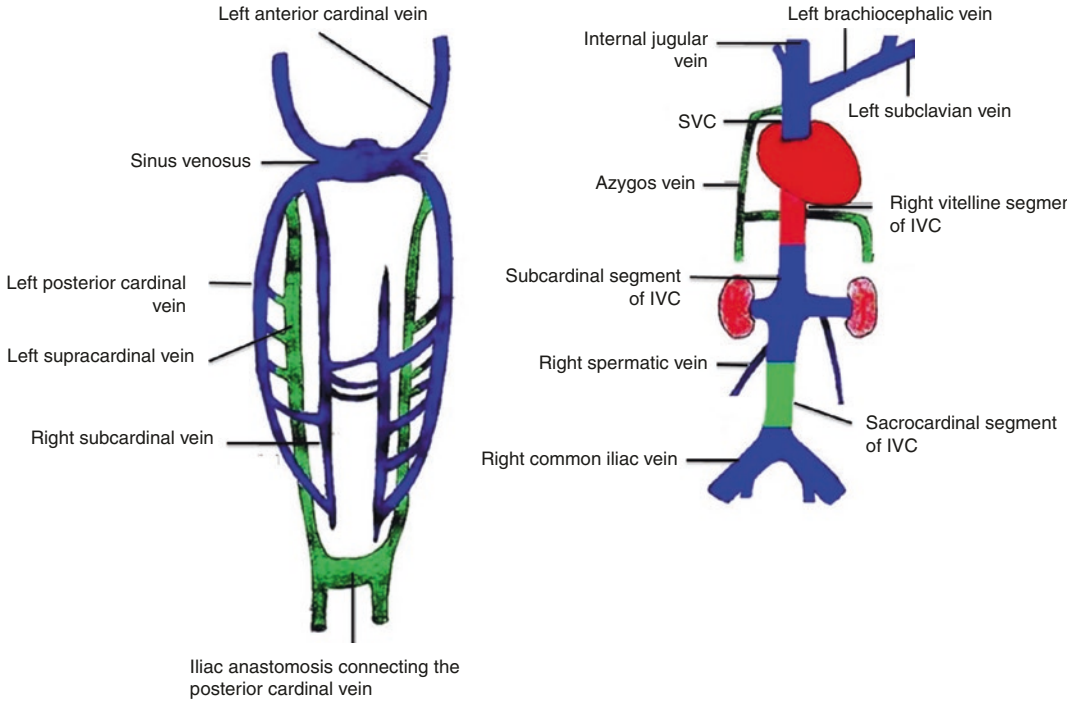

Fig. 14 Illustrations of the primordial veins; initially, three systems of veins are present: the umbilical veins from the chorion, the vitelline veins from the yolk sac, and the cardinal veins from the body of the embryo

wide vascular network. Blood transfer from the left side to the right side of the liver, leads to formation of an expanded right vitelline vein. In the next developmental phases, the right hepatocardiac channel gives origin to the hepatocardiac segment of IVC; but the proximal portion of the left vitelline vein gradually disappears.

The arteries around the duodenum anastomose, then grow as a single vessel called the "portal vein". A small bud of artery grows from the right vitelline vein and creates the superior mesenteric vein. Later on, the distal part of left vitelline vein degenerates.

2. **Umbilical veins** originate from the chorionic villi and transfer highly oxygenated blood from the placenta to the embryo body. During the early stages, a pair of veins, that is, the umbilical veins, pass from both sides of the liver, to connect in later stages to sinusoids of the liver. At this time, the proximal portion of each umbilical vein and the remnants of the right umbilical vein begin to disappear. Therefore, the left vein is the only vein that transfers blood from placenta to the liver. With increased blood flow through the placenta, a direct connection, named ductus venosus is created between the right hepatocardiac channel and the left umbilical veins. Ductus venosus bypasses the sinusoidal plexus in liver. However, obliteration of left umbilical vein leads to ligamentum venosum and obliteration of ductus venosus leads to ligamentum teres.
3. **Cardinal veins** drain the whole embryo body. In the embryonic period, cardinal veins are the early main veins draining the cephalic portion of the embryo. Anterior and posterior cardinal veins are derived from this early venous system; anterior cardinal vein drains the **cephalic** segment of the embryo; while posterior cardinal vein drains the other segments of embryo. These anterior and posterior veins connect together before arriving into the sinus horn, making the **short common cardinal** vein. Throughout the second embryologic month, a considerable number of veins are created including:
   - the sacrocardinal veins which drain the lower limbs,
   - the subcardinal veins which drain the left and right kidneys,
   - the supracardinal veins which drain the body wall.

The anastomosis between the left and right veins leads to development of **vena cava system**; transferring blood from the left side to the right side.

Inferior Vena Cava (IVC) development: the development of IVC occurs during the fourth to eighth gestation weeks. Creation of IVC has many different stages with many developmental complexities, involving all the anatomic venous segments originating from different venous parts (Spentzouris et al. 2014). It was in 1793 that IVC anomalies were first described by Abernethy in a 10 months old baby with concomitant polysplenia and dextrocardia (Petik 2015).

IVC has 4 distinct segments (Spentzouris et al. 2014; Petik 2015; Smillie et al. 2015)**:**

Hepatic IVC: vitelline vein is the origin of the hepatic IVC.

Suprarenal IVC: is originated from right subcardinal vein.

Renal IVC: is created after anastomosis between right subcardinal and right supracardinal veins.

Infrarenal IVC: embryologic development of infrahepatic IVC is the neatly ordered sequence of regression and formation between three paired embryonic veins:

- *subcardinal* veins,
- *supracardinal* veins,
- *posterior cardinal* veins.

The anterior cardinal veins anastomose together and form the **left brachiocephalic** vein. This will lead to an important event in future: *the venous blood drains from the left side of the head and the left upper limbs to the right venous side*. Also, the right common cardinal vein and the proximal part of the right anterior cardinal vein join to make the **superior vena cava**.

The end part of the **left posterior cardinal** vein enters the left brachiocephalic vein; this venous segment is preserved as a small vessel named the **left superior intercostal vein**; venous blood from the second and third intercostal spaces drains into these vessels.

The **left renal vein** is formed by the anastomosis between the subcardinal veins. After that, the left subcardinal vein gradually disappears; only remnants of its distal portion remain which are named the **left gonadal vein**. Therefore, the right subcardinal vein remains as a main drainage channel which forms the **renal segment of the inferior vena cava**.

The sacrocardinal veins merge together and make the **left common iliac veins**. The right sacrocardinal vein forms the **sacrocardinal portion of the inferior vena cava**.

When the renal and hepatic parts of inferior vena cava anastomose together, formation of hepatic, renal, and sacrocardinal segments are completed.

After degeneration of the posterior cardinal veins, the supracardinal veins take the main role in body wall venous drainage. The **azygos vein** is formed after merging of these veins:

- the fourth to 11th right intercostal veins,
- the right supra-cardinal vein,
- part of the posterior cardinal vein.

However, the left fourth to seventh intercostal veins merge and create the **hemiazygos vein** which is drained into the left supracardinal vein; later on, the hemiazygos vein drains into the azygos vein. One should always consider that during the fetal life and later on, until adulthood, there are many anatomical variations of the azygos and hemiazygos veins (Krakowiak-Sarnowska et al. 2003; Keskin et al. 2013; Piciucchi et al. 2014).

The Formation of Lymphatic System

The development of the lymphatic system starts around the end of sixth week, that is, two weeks after recognition of the primordial cardiovascular system. The growth pattern of the lymphatic vessels is much similar to blood vessels. In the final fate of the lymphatic system, there are some connections with the venous system. The early lymphatic capillaries connect with each other to make a lymphatic network (Park et al. 2015).

Development of Lymph Sacs and Lymphatic Ducts

At the end of the embryonic period, there are six primary lymph sacs that include:

- two jugular lymph sacs which are located near the junction of the subclavian veins with the anterior cardinal veins which will be the future internal jugular veins,
- two iliac lymph sacs close to the junction of the iliac veins with the posterior cardinal veins,
- one retroperitoneal lymph sac is located in the root of the mesentery, located on the posterior abdominal wall,
- one cisterna chili located dorsal to the retroperitoneal lymph sac.

In earlier phases, lymphatic vessels create some connections with the lymph sacs and pass along the main veins, in such a way that they create these connections:

- from the jugular lymph sacs to the head, neck, and upper limbs,
- from the iliac lymph sacs to the lower trunk and lower limbs,
- from the retroperitoneal lymph sac and the chyle cistern to the primordial gut; the cistern connects two large channels (right and left thoracic ducts) which are connected to the jugular lymph sacs; later on, between these channels, large anastomosis develops.

The Development of Thoracic Duct

The thoracic duct develops from different parts including:

- the caudal part of the right thoracic duct,
- the anastomosis between the left and right thoracic ducts,
- the cranial part of the left thoracic duct.

Therefore, there are various variations in the origin, course, and insertion of the adult thoracic duct. The right lymphatic duct is created after merging of the right thoracic duct in its cranial part. Both the thoracic duct and the right lymphatic duct join with the venous system at the venous angle which is located between the internal jugular vein and the subclavian vein (Butler et al. 2009; Park et al. 2015).

Circulation Before and After Birth

Fetal Circulation

Prior to birth, the umbilical vein transfer the blood from placenta to the fetus while 80% of its content is oxygen saturated; when blood reaches the liver, it goes directly through ductus venosus into the ***inferior vena cava*** (IVC) in a phenomenon called "short circuiting the liver." A small amount of this blood arrives to the liver sinusoids; then, it is combined with blood coming from the portal circulation. The flow of the umbilical blood via the liver sinusoids is regulated by the sphincter of ductus venosus, located near the entry of the umbilical vein. The sphincter of ductus venosus closes as soon as the first uterine contraction occurs; in order to increase venous entry as much as possible and avoid unexpected overloading of the heart.

The blood coming from the ***placenta*** is well-oxygenated; it comes from the maternal circulation, going through placenta to the umbilical veins and ductus venosus; there, deoxygenated blood coming from the lower limbs is mixed with oxygenated blood; from here, the mixed, though still oxygenated blood is transferred through IVC, going finally to the right atrium.

From this point, part of ***oxygenated blood*** trespasses the foramen ovale to go from right atrium to the ***left atrium***, then left ventricle and aorta to perfuse systemic organs, including brain and heart muscles; which are the first organs receiving well-oxygenated blood coming from placenta.

In addition, the remaining oxygenated blood coming from IVC go through right atrium to the right ventricle, and going to the ***pulmonary trunk*** perfusing the lungs and then, returning through pulmonary veins to the left atrium, left ventricle and descending aorta to go to the to the umbilical artery. However, part of the blood goes through ***pulmonary trunk*** to ductus arteriosus and aorta to flow into the systemic circulation.

Superior vena cava (SVC) drains desaturated blood coming from the arms and head; then, in the left atrium, this blood is combined with desaturated blood coming from the lungs. Afterwards, blood goes into the left ventricle and ascending aorta.

In fetal life, because of high resistance of pulmonary vessels, the majority of blood directly goes from ductus arteriosus to descending aorta and does not pass through pulmonary vessels. In descending aorta, blood is combined with blood coming from the proximal aorta. Finally, desaturated blood goes through descending aorta and then, two umbilical arteries, toward placenta to leave fetal circulation.

As a brief, mixture of saturated and desaturated blood takes places in the following locations:

1. in the **liver**, a small amount of desaturated blood coming from the portal system mixes the saturated blood,
2. in **IVC**, deoxygenated blood returned from the organs such as lower limbs, kidneys, and pelvis is added to the saturated blood,
3. in the **right atrium**, desaturated blood returned from the upper and lower limbs and head is added to the saturated blood,
4. in the **left atrium,** blood returned from the lungs is added to saturated blood,
5. at the junction of **ductus arteriosus** with descending aorta, desaturated blood coming from pulmonary trunk is added to "now *relatively* saturated blood" which finally enters the descending aorta.

Circulatory Alterations after Birth

The events in circulation after birth are discussed in detail in Chap. 3—Pediatric Cardiovascular Physiology. In summary, the fetal circulation shift to a neonatal circulation pattern is an adaptive change in order to tolerate the new "out of the uterus" environment; the final goal is achieving a "***bi-ventricular parallel circulation pattern instead of the series circulation of the fetus***"; here, these steps are discussed in brief (Rabi et al. 2006; Gao and Raj 2010; Katheria and Leone 2012; Noori et al. 2012; Rabe et al. 2012; Duley and Batey 2013; Galinsky et al. 2013; McDonald et al. 2013; Azhibekov et al. 2014; van Vonderen et al. 2014a; van Vonderen et al. 2014b; Baik et al. 2015; van Vonderen and Te Pas 2015; Yigit et al. 2015):

1. establishment of the first inspiratory effort leads to inflation of the lungs and commencement of gas exchange; the result is increased oxygen pressure in pulmonary vascular bed and the alveoli, which is among the earliest initiatives for transition of circulation; as a result, ***pulmonary vascular resistance*** (PVR) drops suddenly in the first 10 min after birth,
2. placental vessels are clamped; abrupt increase in systemic vascular resistance (SVR) happens,
3. foramen ovale is closed due to increased pressure in the left atrial chamber over the right atrial chamber; the mechanism of closure is anatomic relationship between septum primum and septum secundum; however, very shortly afterwards, ductus arteriosus is closed, preventing flow between pulmonary artery and the aorta; this is an essential "shift" in body circulation from a "***series*** circulation" to a "***parallel*** circulation,"
4. complete anatomical closure of foramen ovale and ductus arteriosus occurs later; often, foramen ovale is closed physiologically first, and then, anatomically during a few days, with a minority having only physiologic closure of foramen ovale even in adulthood; however, ductus arteriosus is closed during the first 48–72 h after birth,
5. umbilical vein stops its venous flow at birth,
6. portal venous system pressure increases, leading to redirection of flow through the hepatic veins,
7. ***β receptors*** are not as much frequent in the newborn heart; but they increase in myocardium after birth,
8. this transitional circulation needs a minimum of 5 min during the first stages of life; resulting in the "***normal postnatal*** oxygen saturation" state,
9. blood pressure in the early postnatal period depends on a number of factors; mainly cardiac output (CO) and systemic vascular resistance (SVR); in addition, these factors affect blood pressure: neonatal asphyxia, drugs transferred from the mother like antihypertensive agents or some anesthetics; term infants versus preterm infants; vaginal delivery compared to cesarean section and gender (female vs. male neonates).
10. cardiac output considered as left and right heart output assumes the "normal" pattern after birth; in fact, in the fetal circulation, the main load of cardiac output is on the right heart; however, just after birth, that is, in the postnatal period, while the transition from series circulation to parallel circulation ensues, left ventricle and right ventricle cardiac output equalize and the dominancy of right ventricle output (RVO) disappears and at the same time, left ventricle output (LVO) and left ventricle stroke volume (SV) increase; also, cardiac output increases in the early postnatal 2–5 h while after that, due to closure of ductus arteriosus, cardiac output gradually drops to a bit lower levels to become stable.
11. if any pathology impairs this process, the transition from fetal to neonatal circulation does not occur correctly, leading to **persistence of fetal circulation**,
12. increased PVR due to hypoxia, acidosis and hypercarbia, history of diabetes in mother during pregnancy, intrauterine inflammation due to infection or other reasons, increased pressure in the right atrium over the left atrium leading to impaired closure of fora-

men ovale, or patency of ductus arteriosus are among the main etiologies for ***persistence of fetal circulation***.

Angiomas

Abnormal and unnecessary growth of small capillary networks is named a capillary hemangioma. On the other side, accumulating and germinating bundle of large venous sinuses is a cavernous hemangioma. Infantile hemangiomas are the most common vascular tumors in childhood. These tumors develop rapidly and cause an uncontrolled growing mass composed of endothelial cells, lumen obstruction, multilayered basement membranes, and fibrous tissue. Their only risk is when they are located on critical anatomical points like skull or vertebral canal, or in the airways (Marler and Mulliken 2005).

Genetic basis, linked with developmental syndromes or chromosomal abnormalities, has been proposed for some hemangiomas. For example:

- 5q31–33 of chromosomal region has close link with some hemangioma, containing genes such as FGF4, PDGFβ, and FMS-RELATED TYROSINE KINASE, coding the molecules essential in blood vessel growth,
- dysregulation of the TIE/ANG signaling pathways,
- mutations of VEGFR2,
- multiple hemangioblastomas are related with von Hippel - Lindau disease, with mutations in a gene at chromosome 3p25-26,
- excessive angiogenesis may be due to great levels of vascular endothelial growth factor (VEGF) and Hypoxia Inducible Factor 1 Alpha (HIF1α) secretion by stromal tumor cells.

Abnormalities of the Ductus Arteriosus

The ductus arteriosus which located in the right side of aortic arch grows toward the right side either in front or behind the esophagus and trachea, making ligamentum arteriosum after its postnatal closure.

If it passes from behind of the esophagus, it can lead to a constriction of esophagus and trachea with clinical dysphagia and/or dyspnea.

When the right and left fourth aortic arches are disappeared and the distal right of dorsal aorta persists, a disease state known as interrupted aortic arch happens. After birth, the aorta supplies the upper body, upper limbs, and head, but the pulmonary artery which contains blood with poorly oxygenated blood supplies the lower body and limbs through a patent ductus arteriosus. Detailed discussion about interrupted aortic arch could be found in Chap. 28.

Aortic Coarctation

Coarctation of aorta (CoA) is one of the common congenital defects, more common in males than females. CoA is may occur as a separated abnormality or in association with various other injuries, usually bicuspid aortic valve (BAV) and ventricular septal defect. The disease is discussed in Chap. 28.

CoA is often defined as a restricted aortic segment encompassing localized medial thickening, with some enfolding of the medial and overlaid neointimal tissue.

The underlying mechanism for aortic coarctation is still controversial, although the deformity may be initiated by genetic factors or by teratogens.

There are two main potential etiologies proposed as the causative mechanism for CoA; namely "*ductal* theory or *ductus tissue* theory" and "*hemodynamic* theory or *flow* theory," described as follows:

- *hemodynamic* theory or *flow* theory: more widely accepted, this theory known as "***Rudolph theory"*** states that during the fetal period, the development of the aortic arch (including the length and the diameter of the arch) depends on "*the amount of blood flow which passes through the arch*"; if this blood flow is impaired leads to a narrowed and/or hypoplastic aortic arch, this

phenomenon explains three main features of CoA: (1) the "*posterior shelf*" (2) the "*intracardiac defects*" which are concomitant embryologic lesions (3) "*tubular hypoplasia*" which is often a concomitant lesion of CoA; (4) the right-sided obstructive lesions which are very rarely associated with CoA,

- *ductal* theory or *ductus tissue* theory: this theory is also known as "***Skodaic hypothesis"*** assumes "abnormal distribution or aberrant migration" of Smooth Muscle Cells (SMC) from ductus arteriosus to the adjacent aortic tissue as the etiology of CoA; in other words, ectopic ductal tissue in the aortic isthmus causes CoA and aortic constriction, usually in the isthmus of aorta (i.e., the junction of aorta with ductus arteriosus) (Krediet 1965; Gillman and Burton 1966; Hutchins 1971; Heymann and Rudolph 1972; Rudolph et al. 1972; Shinebourne and Elseed 1974; Moore and Hutchins 1978; Ho and Anderson 1979; Momma et al. 1982; Meurs-Van and Krediet 1982; Russell et al. 1991; Jimenez et al. 1999; Liberman et al. 2004; Carroll et al. 2006; Kenny and Hijazi 2011).

CoA occurs in three forms:

- juxtaductal location which is close to the ductus arteriosus and is more common than other forms,
- preductal CoA, that is, proximal location which is upstream of ductus; usually, collateral circulation does not develop, since the ductus arteriosus connects most of the oxygen- and nutrient-enriched blood from the placenta to the lower portion of the body (Fig. 15),
- postductal CoA, that is, distal location which is downstream of ductus; postductal CoA is asymptomatic in some newborn infants, since other arteries including subclavian, internal thoracic, transverse cervical, suprascapular, superior epigastric, intercostal, and lumbar arteries create collateral circulation throughout the embryonic and fetal period (Fig. 15).

When the ductus is closed after birth, the infants suffering from CoA are imposed with many abnormalities. In this disease, the upper part of the body and head is well perfused, but the lower part is somewhat ischemic. CoA repair may be done by surgery, stenting or balloon dilation angioplasty with different outcomes and chance of recurring stenosis. More detailed discussion on this topic is provided in Chap. 28 of this book.

Alagille syndrome refers to genetic problems that result in various symptoms in different parts of the body, including the liver, kidney, heart, and other systems of the body such as paucity of bile ducts and arterial stenosis. Abnormalities related to the disorder generally become apparent in early childhood or infancy .

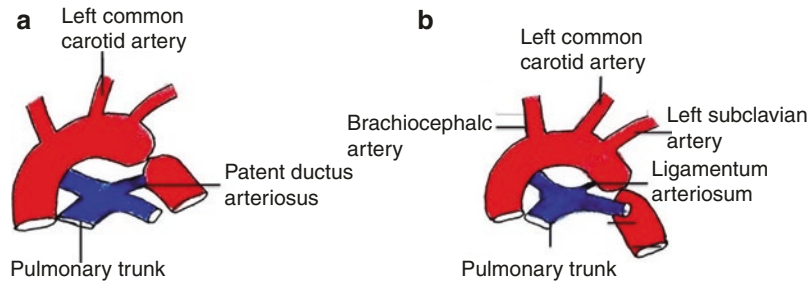

Fig. 15 Coarctation of aorta; (**a**) Preductal type; (**b**) Postductal type

Vena Cava Anomalies

The anomalies of venae cavae are categorized as predicted under two main classes: IVC anomalies and SVC anomalies.

IVC Anomalies

Inferior vena cava (IVC) anomalies were first described in 1793 by Abernethy in a 10 months old baby who had polysplenia and dextrocardia (Petik 2015).

Embryologic development of IVC is the neatly ordered sequence of regression and formation between three paired embryonic veins (Fig. 14):

- subcardinal veins,
- supracardinal veins,
- postcardinal veins.

As mentioned in the previous pages, under IVC development, these events occur between the fourth and eighth gestational weeks, in a multi-stage process; so, embryologic development of IVC is a potential process for many developmental malformations. Since the development of cross-sectional imaging, congenital anomalies of the IVC and its side streams have been encountered much more frequently, and in a large number of affected patients, these anomalies have been symptom free.

Congenital anomalies of IVC are diverse and at least, 14 types of anomalies have been reported till now; among these 14, the most important ones are these four types (Srivastava et al. 2005; Dutta 2010):

- double IVC; also known as duplication of IVC,
- left IVC or left-sided IVC,
- retroaortic left renal vein,
- circumaortic left renal vein.

Among the other lesions are interrupted IVC, other left renal vein anomalies, gonadal vein anomalies, preduodenal portal vein (Malaki et al. 2012; Latha et al. 2014; Hagans et al. 2014; Spentzouris et al. 2014; Petik 2015).

Persistent left IVC is usually the result of two events which happen together: "***regression of the right supracardinal veins plus persistence of the left supracardinal veins***".

The typical form of persistent left IVC is that it will merge with the left renal vein, then, crosses to the other side, reaching the right renal vein, anterior to the aorta; this crossover from left to right is almost always at the level of renal veins. The final result is a normal right sided IVC which is located in prerenal position (Bass et al. 2000; Malaki et al. 2012; Petik 2015).

There may be two forms of azygos continuation of IVC:

- left IVC and absent infrarenal IVC with azygos continuation of IVC,
- left IVC and absent infrarenal IVC with azygos and hemiazygos continuation.

Double IVC is a rare anomaly; its etiology is failure of regression in the caudal part of the left supracardinal veins, leading to persistence of ***both supracardinal veins*** and creation of an abnormal left IVC accompanied with right IVC; hence, there will be two IVCs. Significant asymmetry between the sizes of right and left IVC's is possible. Venous blood arriving left IVC will ultimately drain into one of the following veins:

- right IVC via the left renal vein,
- hemiazygos vein rising from thoracic part of the supra-cardinal system (Bass et al. 2000; Malaki et al. 2012).

SVC Anomalies

Left Superior Vena Cava

In some patients, the left anterior cardinal vein remains, leading to preserved connection between anterior cardinal vein and the left sinus venosus. Its incidence in general population is about 0.3 to 0.5%. If left SVC persists, blood coming from

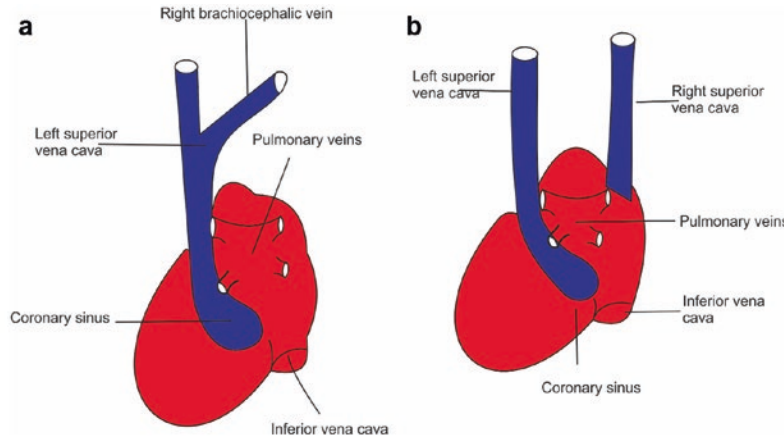

Fig. 16 Left SVC; (**a**) Doubled SVC; (**b**) left SVC

the left side of the head, neck, and the upper extremity are emptied through the abnormal left SVC into the coronary sinus. This anomaly is presented either as a steady left (double) SVC or a single left SVC. A single left SVC is seen if the left anterior cardinal vein persists while at the same time, the right one is eliminated. In this situation, the left anterior cardinal vein leads to a superior vena cava draining the blood from the entire head and neck, both upper extremities, and the azygos system, then directing all this venous blood into the coronary sinus and right atrium. However, when double and left SVC are present, left SVC drains directly into the left atrium; this condition is seen more commonly in heterotaxy cases (Fig. 16). In about 65% of all left SVC cases, the left brachiocephalic vein is either very small or does not exist at all.

Lymphatic System Anomalies

Lymphedema may result from lymphatic hypoplasia. Primary lymphedemas also known as lymphatic obstruction are swellings of the lymphatic vasculature and a major hereditary congenital disorder of the lymphatic system which are induced by hypoplasia of the lymphatic system. This condition usually is accompanied with other abnormalities. There are a number of genes involved in the development of lymphedema (Dellinger et al. 2008; Stoll et al. 2013; Sabine and Petrova 2014; Yang and Oliver 2014; Park et al. 2015):

- FOXC2 gene.
- the transcription factors related to the Forkhead family,
- SOX18 gene mutations and SRY-related transcription factor.
- Ang2, Nrp2, Net, Podoplanin, and Syk.

The most severe swellings usually take place in the legs but, for lymphedema related to **Turner syndrome**, the lymphatic ducts are obstructed in the neck region and upper trunk; however, this clinical feature may also be the result of lymph-filled cysts development (known as cystic hygromas). These cysts may withdraw if drainage of lymphatic recovers during subsequent stages of development.

Milroy disease is associated with impaired function of the lymphatic system; so, it is a primary lymphedema syndrome due to mutations in the VEGFR3 gene.

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Pediatric Cardiovascular Physiology

Ali Dabbagh, Alireza Imani, and Samira Rajaei

Abstract

Cardiac physiology is the underlying mechanism of the cardiovascular system which works in a beat-to-beat manner, especially in patients with congenital heart diseases. This field has improved significantly as a result of the developments in cellular and molecular medicine. In this chapter, after an introductory discussion about the *evolutional transition in cardiac physiology* from fetal to neonatal, childhood, and adulthood, the myocardial function has been presented with its three main ingredients: electrical function of the myocardium, excitation-contraction coupling, and mechanical function of the myocardium. Control mechanisms of cardiac function including receptors, signals, and neurohormonal pathways are among the most important controlling mechanisms in the human body which are described afterward.

Developmental changes in fetal cardiac muscle are mandatory for anyone who wants to work with patients having congenital heart disease; a full discussion could be reached in the previous chapter of the book.

Cardiac work includes the normal sequences in the cardiac cycle, the Frank-Starling relationship, and the factors involved in cardiac work which are described next.

And finally, the cardiac reflexes are described which are another main controller of cardiovascular physiologic response.

Keywords

Cardiovascular physiologic · Pediatric Congenital heart diseases

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Evolutional Transition in Cardiac Physiology

The physiologic change from fetal to neonatal circulation constitutes two main items that have several main impacts: lack of lung ventilation in fetus and the "series" model of circulation. A number of these are discussed here more; however, some of the other developmental changes, especially those related to contractile processes, are discussed in the next parts of this chapter.

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Fetal Circulation and Its Developmental Changes

1. Lungs are not ventilated in the fetus; so, pulmonary vessels are nearly collapsed having a very high vascular resistance, leading to only about 10% of the cardiac output through the lungs.
2. The placental vessels have a very low resistance leading to a highly perfused vascular bed in the fetal circulation.
3. The main gas exchange is through the placental vessels.
4. The blood circulation does not follow two parallel circuits; instead, one circulation pathway exists and the blood flows through a "series" circuit to perfuse all the organs; complete mixing occurs through ductus arteriosus, foramen ovale, umbilical vessels, and placental vessels.
5. The right and left ventricles (RV and LV) are connected through the foramen ovale and so, there is not a significant pressure difference between the two chambers; the right ventricle has a greater workload (about 2/3 of the heart workload is tolerated by RV and 1/3 by LV).
6. The deoxygenated blood inside the superior vena cava (SVC) passes the right atrium to the right ventricle and then, goes through the ductus arteriosus to the descending aorta; however, the deoxygenated blood does not go to the pulmonary vascular system due to its high resistance.
7. Oxygenated blood comes from the placenta to pass the inferior vena cava (IVC) and then goes through the foramen ovale, left atrium, and left ventricle to the ascending aorta to perfuse all body organs.
8. Finally, when assessing the fetal circulation as a whole, there are three main shunts in the fetal circulation:
   (a) **Ductus venosus**: oxygenated blood passes from the umbilical vein to the inferior vena cava.
   (b) **Foramen ovale**: blood from the right atrium through the foramen ovale inter into the left atrium.
   (c) **Ductus arteriosus**: blood from the pulmonary artery (due to the high resistance) passes through the ductus arteriosus to the aorta and then returned to the placenta for oxygenation through the umbilical arteries (Hines 2013; Azhibekov et al. 2014; van Vonderen and Te Pas 2015; Dyer and Rugonyi 2021).

Changes in Circulation at Birth

The fetal circulation should be changed to a neonatal circulation pattern to adapt to the new environment out of the uterus; this is an obligatory change that is achieved through some sequential events in the circulation; these events are well ordered and delicately arranged, one after the other, to achieve the goal of "transition" and achieving a "bi-ventricular parallel circulation pattern" instead of the series circulation in the fetus. The main bulk of our knowledge regarding this human neonatal transition is based on human fetal data from studies performed in the 1970s; however, animal studies have been added to them; during recent years, cellular and molecular studies have elucidated part of the underlying mechanisms which have led to new windows in the treatment of the resulting abnormalities; a summary of these studies is presented here as the following transitional physiologic steps (Rabi et al. 2006; Gao and Raj 2010; Katheria and Leone 2012; Noori et al. 2012; Rabe et al. 2012; Duley and Batey 2013; Galinsky et al. 2013; McDonald et al. 2013; Azhibekov et al. 2014; van Vonderen et al. 2014a, b; Baik et al. 2015; van Vonderen and Te Pas 2015; Yigit et al. 2015; Bentley et al. 2021; Dyer and Rugonyi 2021):

1. Lungs are inflated and the gas exchange starts, with the resultant increase in the oxygen pressure of the pulmonary vascular bed and the alveoli; this would be one of the very crucial and among the earliest initiatives for the transition of circulation; so, as a result, ***pulmonary vascular resistance*** (PVR) drops suddenly and significantly during the first

10 min after birth which will result in a rapid surge in pulmonary blood flow.

2. Placental vessels are occluded after cord clamp leading to an abrupt increase in systemic vascular resistance (SVR); This is probably due to thermal and mechanical stimulation and an alteration in oxygen tension; in addition, the contraction of the smooth muscles in the wall of the umbilical arteries causes their closure, which usually occurs a few minutes after birth, though the real destruction of the lumen by fibrous proliferation may happen 2 to 3 months later; the distal portion of umbilical artery forms the medial umbilical ligaments and the proximal portion of umbilical artery stay open, making the superior vesical arteries; however, just following the closure of the umbilical arteries, the ductus venosus and umbilical veins are also closed; this is why blood could enter from the placenta to the newborn circulation for a short time interval after birth. Following obliteration, the ligamentum teres hepatis is formed from the umbilical vein.
3. With the increased pressure in the left atrial chamber over the right atrial chamber, the foramen ovale is closed and also, in a very short time, the ductus arteriosus is closed; closure of ductus arteriosus leads to flow reversal in the ductus, which prevents any further flow between the pulmonary artery and the aorta; this is an essential "shift" in body circulation: in other words, the circulation changes from a "***series*** circulation" to a "***parallel*** circulation."
4. The complete anatomical closure of ***foramen ovale*** and ***ductus arteriosus*** is not abrupt; in fact, *foramen ovale* is closed physiologically first, and then, it will be closed anatomically during a few days; however, there are a minority of "normal" children in whom, foramen ovale is not closed anatomically even till adulthood, leading to the potential opening of foramen ovale in case of increased pulmonary vascular resistance and the possibility of right-to-left embolization; on the other hand, ductus arteriosus is closed during the first 48–72 h after birth; on the other hand, *ductus arteriosus* is closed directly after birth due to contraction of the neighboring muscles; here, bradykinin (a substance released from the lungs after early inflation) plays the main role in contraction and closure of ductus. It is estimated that the anatomical obliteration of ductus arteriosus by the proliferation of its intima takes about 1 to 3 months. In the adult period, the ligamentum arteriosum is formed by the obliteration of ductus arteriosus.
5. Venous flow from the umbilical vein stops at the time of birth; also, the muscular contraction causes the ductus venosus to be closed; ligamentum venosum is formed after the closure of ductus venosus.
6. Pressure in the portal venous system increases, which leads to redirect flow through the hepatic veins.
7. Throughout this transitional period, there is a marked increase in blood levels of stress hormones including catecholamines, and activation of renin-angiotensin-aldosterone level.
8. ***β receptors*** are not as frequent in the newborn heart as in the adult heart; however, after birth, several factors lead to increased levels of β receptors in the myocardium; the effect of thyroid hormone is of great importance.
9. In a normal newborn, at least the first 5 min of life are needed to pass the transitional circulation and to reach the "***normal postnatal*** oxygen saturation" state according to the following order.
   (a) Just in the 1st minute of life: blood oxygen saturation is about "60–70%".
   (b) During the first 5 min of life, the oxygen saturation increases to "80–90%".
   (c) And finally, in the first 10 min of life, blood oxygen saturation increases to more than 90%.

The above trend in oxygen saturation demonstrates the "***normal shift***" from fetal to neonatal circulation; all these saturation levels are somewhat lower after cesarean delivery compared with normal vaginal delivery. There are some controversies regarding the effect of delayed umbilical cord clamping on neonatal physiology and the transition from fetal to neonatal physio-

logic status; currently, the available evidence is toward delayed cord clamping since it would improve the neonatal hemodynamics and blood volume accompanied by "sustained placental respiration" (Rabi et al. 2006; Noori et al. 2012; Azhibekov et al. 2014; Bentley et al. 2021; Dyer and Rugonyi 2021; Sharma et al. 2021)

1. Blood pressure in the early postnatal period depends on cardiac output (CO) and systemic vascular resistance (SVR); meanwhile, in the neonatal period, these factors affect blood pressure.
   (a) Neonatal asphyxia decreases blood pressure.
   (b) Some drugs decrease blood pressure (like antihypertensive drugs used in mothers or mothers receiving some anesthetic drugs for cesarean delivery).
   (c) Blood pressure is higher in preterm infants compared to term infants.
   (d) Blood pressure is higher in neonates after vaginal delivery compared to cesarean section.
   (e) Blood pressure is higher in female neonates compared to male ones (Baik et al. 2015).
2. Cardiac output considered as left and right heart output assumes the "normal" pattern after birth; in the fetal circulation, the main load of cardiac output is on the right heart; however, just after birth, that is, in the postnatal period, while the transition from series circulation to parallel circulation ensues, left ventricle and right ventricle cardiac output equalize and the dominancy of right ventricle output (RVO) disappears and at the same time, left ventricle output (LVO) and left ventricle stroke volume (SV) increase; also, cardiac output increases in the early postnatal 2–5 h while after that, due to closure of ductus arteriosus, cardiac output gradually drops to a bit lower levels to become stable (van Vonderen et al. 2014a; Baik et al. 2015; Vrancken et al. 2018).
3. Several associated problems could affect the process of transition from fetal to neonatal circulation and hence, cause some delay or even impairment in the process of normal transition leading to **persistence of fetal circulation**, among them, the following could be mentioned (Vrancken et al. 2018; Bentley et al. 2021; Sharma et al. 2021).
   (a) Any kind of impairment in pulmonary circulation which could increase the pulmonary vascular resistance (PVR); hypoxia, acidosis, and hypercarbia may lead to pulmonary vasoconstriction and increased PVR.
   (b) Increased pressure in the right atrium over the left atrium could lead to reopening of foramen ovale which would severely exacerbate the right to left shunt and aggravate the unwanted phenomenon of "**persistence of fetal circulation"**; if closure ductus arteriosus also does not happen, the persistence of fetal circulation goes much worse, which may mandate surgical intervention to treat persistence of fetal circulation (Bentley et al. 2021; Dyer and Rugonyi 2021).
   (c) History of diabetes in mother during pregnancy.
   (d) Intrauterine inflammation due to infection or other reasons.

Myocardial Electromechanical Function

To produce lifelong cardiac output, the heart needs to initiate electrical activity, disseminate it in a well-designed and sequential manner to all parts of the heart, and produce cardiac output as "projectile" stroke volume in each beat using a dynamic interaction of underlying cardiac factors (Jeon et al. 2020). However, if we want to analyze the physiologic job of the heart, we will have to understand the three following as the main cardiac tasks; these functions when integrated could produce the global physiologic function of the heart. However, for these tasks to be done, specialized cells are arranged delicately (Xin et al. 2013; Mackrill and Shiels 2020):

1. Electrical function (due to action potential) of the heart; mainly though pacemaker cells and Purkinje fibers (these are specialized cardiomyocytes that we call them together with the conductive cells; they generate and conduct the electrical impulse).
2. Excitation-Contraction Coupling (ECC) is the intermediary step between electrical and mechanical activities of the myocardium, which is done by a complex of cellular systems inside the myocardial syncytia.
3. The mechanical (contractile) function of the myocardium is performed after a series of sub-functions between contractile proteins which initiate, modulate, and terminate each cardiac contraction and relaxation, that is, systole and diastole; the contractile function is the role of atrial and ventricular cardiomyocytes, which form the cardiac muscular segment; however, they are supported by the integration of connective tissue and cardiac fibroblasts.

These physiologic jobs are done mainly through two important cardiac syncytia:

1. ***Atrial syncytium*** which is composed of the myocardial tissue of left and right atria, plus inter-atrial septum and sinoatrial node (SA node).
2. ***Ventricular syncytium*** which is composed of the myocardial tissue of left and right ventricles, the interventricular septum and atrioventricular node (AV node), atrioventricular bundle, and the other conducting structures distal to the AV bundle.

On the other hand, the function of the heart is performed in a two-time domain: systole and diastole. In systole, the contractile function of the ventricular syncytium causes blood pumping during an ejection process which is associated with blood pumping out of the ventricles: aortic and pulmonary valves are open, and mitral and tricuspid are closed. On the other hand, in diastole, the ventricles expand in an active process leading to the return of blood from atria to related ventricles; mitral and tricuspid valves are open while aortic and pulmonary valves are closed (Fig. 1).

Here, we discuss the three main myocardial roles in more detail (i.e., electrical function, ECC, and contractile function)

Electrical Function of the Myocardium: Action Potential

The electrical part of cardiac function is done through a well-organized and highly specialized

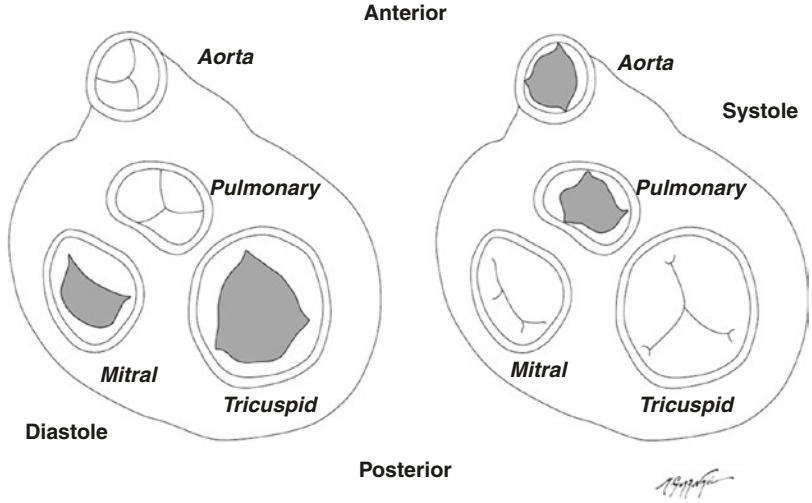

Fig. 1 The apex of the heart when viewed from above in systole and diastole; note the position of the valves and their relationships. (Modified from Dabbagh A. "Cardiac physiology"; in "Postoperative Critical Care for Cardiac Surgical Patients". Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp 1-39. Published with kind permission of)

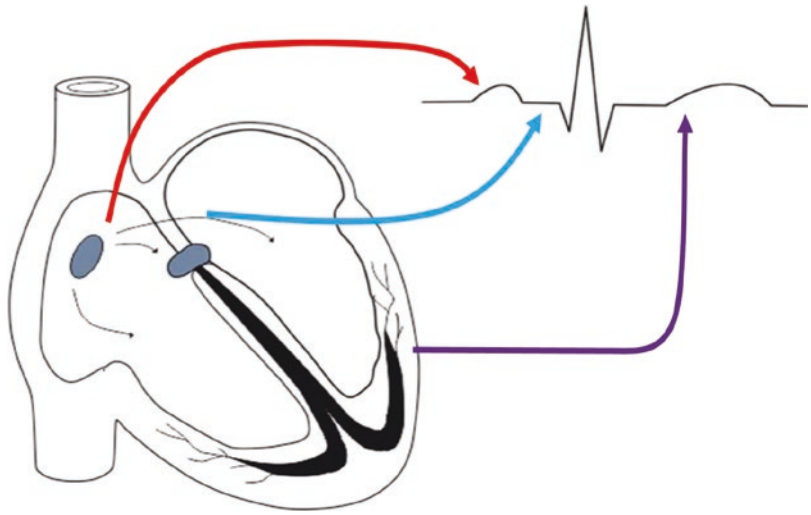

Fig. 2 Cardiac conductive system and its elements; on left, see the relationship of normal electrocardiography with the elements of the system. (Modified from Dabbagh A., et al. "Cardiac physiology"; in "Postoperative Critical Care for Cardiac Surgical Patients". Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp 1-39. Published with kind permission of © Springer, 2014. All Rights Reserved.)

"***electrical network***"; this network has two main cell types (Fig. 2):

1. "Impulse generating cells" which have an excitatory function and produce impulse; these cells mainly compose ***sinoatrial (SA) node***

   The SA node lies in the cephalic portion of the posterior wall of the right atrium just near the orifice of SVC. SA node has a complex architecture leading to heterogeneous electrical activity throughout the SA node. Also, pacemaking cells, especially in SA node, have some specific specifications:
   (a) Higher rate of spontaneous beating.
   (b) Faster activation of the funny current (I_f) which is described later.
   (c) Greater density of the funny current (Mikawa and Hurtado 2007).
2. "Conductive cells" which are a well-defined network for conduction of the impulse and are composed of:
   (a) Atrioventricular (AV) conduction pathways.
   (b) Atrioventricular (AV) node which lies just superior to the endocardial cushions, in the inferior part of the interatrial septum, and anterior to the coronary sinus foramen.
   (c) The *His bundle.*
   (d) The right and left branches of His bundle.
   (e) The network of "*Purkinje fiber cells*" also known as the "*Purkinje fiber network*"; the Purkinje fiber network is an extension of the Hiss bundle distributed all over the ventricular tissue; in such a way to propagate and conduct the electrical impulse throughout the ventricles as fast as possible (Desplantez et al. 2007; Dun and Boyden 2008; Atkinson et al. 2011; Sahli Costabal et al. 2016; Oh et al. 2018).

Action Potential in Cardiac Cells

Certain ions, ion currents over both sides of the myocardial cell membrane, and the cell membrane itself (including its integral structures like membrane channels, receptors, and enzymes), and also, some internal cell structures work together to produce the electrical activity of myocardial cells. Electrical activity achieved as a result of different ion currents (Na^+, K^+, and Ca^{2+}) and activation of certain receptors or enzymes can alter this activity. The ion currents have the main role and other factors like sympathetic and parasympathetic effects do not exert roles in the generation of action potential; if we denervate the heart of an animal in the lab, action potential and impulse generation would not be stopped, but can

affect the generation and shape of the action potentials.

Generation of the action potential is essential for producing mechanical activity in the muscular wall of atria and ventricles, depolarization for contraction, and repolarization for relaxation. For this, the action of the heart is called electromechanical activity.

Generally, there are two types of action potential in the heart, a fast response action potential in the myocardium and Purkinje system and a slow response action potential in nodal cells. Myocardial action potential consists of five sequential phases: Phase 0 to Phase 4. These phases compose together the electrical wave of myocardial cells known as action potential: "**AP,**" which are described herein in Table 1 and Fig. 3.

Cardiac Automaticity and Its Mechanism(s)

How does the pacemaker activity in the cardiac cells happen? For answering this question, we should look for the main difference between "myocardial cells" and "pacemaker cells" regarding action potential.

Action potential (AP) in cardiac pacemaker cells: although the main mechanisms in AP of cardiac pacemaker cells are similar to those in myocardial cells, there are some differences:

1. ***Resting membrane potential*** in pacemaker cells is higher than in myocardial cells; that is, resting potential is about −90 to −80 in myocardial cell population; instead it is about −60 to −50 in cardiac pacemaker cells; one of the main mechanisms for this upper level of resting potential in pacemaker cells is Na^+ influx during repolarization known as the funny current abbreviated as **I(f)** (DiFrancesco and Noble 2012; Papaioannou et al. 2013; Weisbrod et al. 2013; Aziz et al. 2018; Oh et al. 2018; Joukar 2021)
2. There are two main Ca^{2+} channels in heart tissue: T (Transient) type Ca^{2+} channels (abbreviated as $\boldsymbol{I}_{CaT}$) and L (Long lasting) type Ca^{2+} channels (abbreviated as $\boldsymbol{I}_{CaL}$); both $\boldsymbol{I}_{CaT}$ and $\boldsymbol{I}_{CaL}$ are categorized under voltage gated Ca^{2+} channels (VGCC) and have their role in impulse generation (i.e., SA node) and atrioventricular impulse conduction (i.e., AV node); though $\boldsymbol{I}_{CaT}$ typically diminishes in normal adult heart, they have active role in the final segments of repolarization and play their role in combination with *I*(f) to produce prepotential steep which is in fact the "***pacemaker potential***"; $\boldsymbol{I}_{CaT}$ has two isoforms in cardiac tissue: Ca(V)3.1 and Ca(V)3.2; also, Ca(V)1.3 is the main isomer of $\boldsymbol{I}_{CaL}$ in heart; Mesirca et al. expressed that severe forms of congenital bradycardia and atrioventricular

Table 1 Action potential in myocardial cells

Phase	The event in action potential	Ion current	Electrical status (mV)
Phase 0	Rapid upstroke: *Depolarization*	Na^+ influx	Starts from −90 to −80 and goes up to about +10 to +15
Phase 1	Very short and initial *repolarization* which is "Incomplete repolarization"	K^+ outflux	Starts from +10 to + 15 and decreases to about +5
Phase 2	Initiation of contraction due to Ca^{2+} influx; this phase is also titled "*Plateau*" Usually determines the *action potential duration* and also, the *refractory period*	Ca^{2+} influx due to opening of slow (L) type Ca^{2+} channels; also, K^+ outflux	Starts from + 5 and has a nearly steady level; maximum drop to 0
Phase 3	*Final Repolarization*	Huge K^+ outflux	Starts from about "0" Ends at −80 to −90
Phase 4	Resting potential, that is, no active potential)	K^+ influx and outflux	Stays at −80 to −90

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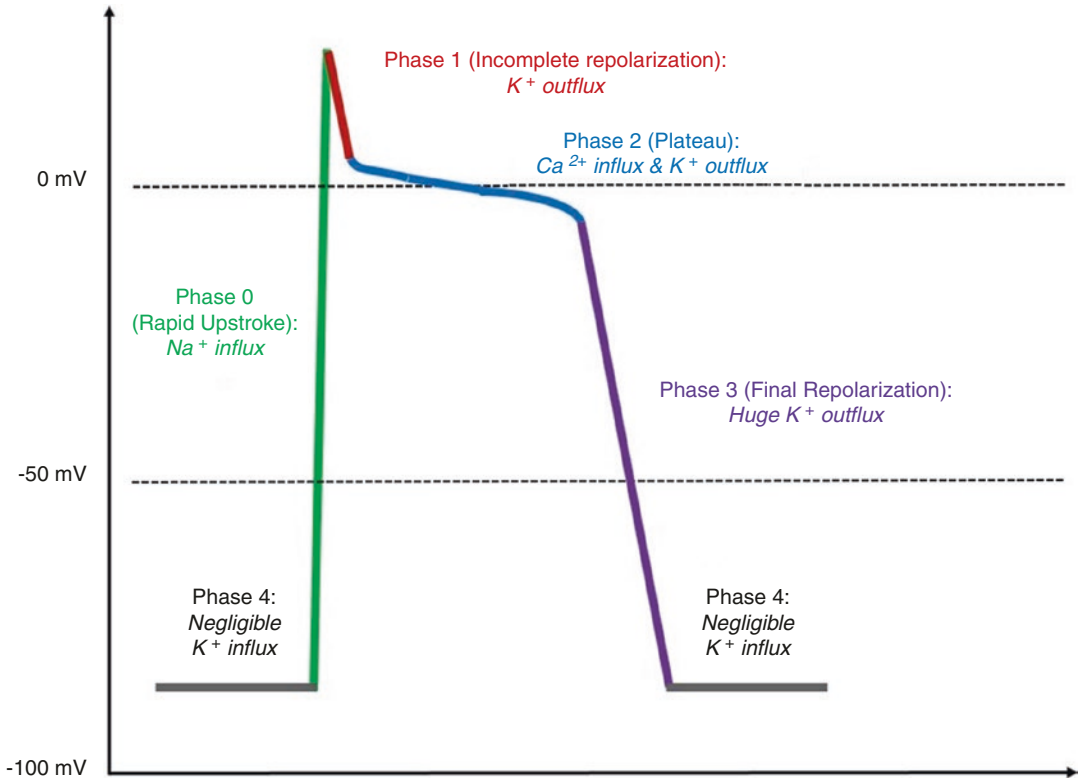

Fig. 3 Progress of action potential phases. (Modified from Dabbagh A., et al. "Cardiac physiology"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management". Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp 65-116. Published with kind permission of © SpringerNature, 2017. All Rights Reserved (Marcotti et al. 2004; Parham et al. 2006; Wolf and Berul 2008; Amanfu and Saucerman 2011; Marionneau and Abriel 2015))

block in pediatric patients are associated with functional loss of Ca(V)3.1 isomer of $\boldsymbol{I}_{CaT}$ receptors; however, all types of VGCC, Ca(v)1.2, mediate excitation-contraction coupling which is a crucial process in contractile function and discussed later in the chapter (Sobie et al. 2006; Ono and Iijima 2010; Mesirca et al. 2014, 2015; Aziz et al. 2018; Joukar 2021)

3. In cardiac pacemaker cells, the slope of AP in phase 4 is not as flat as in myocardial cells, instead, it is upward, known as the ***prepotential steep phase,*** and is mainly due to three main factors (Hoekstra et al. 2021):
   (a) Funny current: *I*(f)
   (b) Ca^{2+} influx by $\boldsymbol{I}_{CaT}$
   (c) K^+ efflux by potassium channel ($\boldsymbol{I}_K$)
4. On the other hand, the main role of $\boldsymbol{I}_{CaL}$ is in Phase 0; in pacemaker cells (SA node and AV node), $\boldsymbol{I}_{CaL}$ exerts its main role in Phase 0 or depolarization, and "Ca^{2+} influx" in pacemaker cells replaces "Na^+ influx" of myocardial cells
5. Phase 1 (i.e., short-term repolarization) is nearly deleted or better say, integrated into phases 2 and 3
6. Both phase 2 and phase 3 are merged to create a downhill in repolarization; so, there is no sensible plateau; instead, we see phases 1, 2, and 3 as a single repolarization phase which is terminated by phase 4. A summary of these phases is demonstrated in Table 2 and Figs. 4 and 5.

There is another important concept in the action potential of many cells including myocar-

Table 2 Action potential in cardiac pacemaker cells

Term (phase)	The event in action potential	Ion current	Electrical status (mV)	The difference with myocardial AP
Phase 0	Depolarization	Ca^{2+} influx by I_{CaL}	Start from threshold level (−40) and goes up to about 0 to +5	Its slope is slower than phase 0 in cardiomyocytes
Phase 1	Nearly *deleted and Integrated* in phases 2 and 3			
Phase 2	No sensible "*Plateau*": merged with phase 3 as a "Single Repolarization phase"			
Phase 3	*Repolarization*	K^+ efflux	Starts from about "0 to +5"; ends at −50 to −60	Merged with phase 2 as a single "Repolarization phase"
Phase 4	Resting potential (Steep prepotential)	I(f): Funny current Ca^{2+} influx by I_{CaT} K^+ efflux by I_K	Potential level increases from −50 or −60 to the threshold level (−40)	Unlike the stable phase in cardiomyocytes, is unstable and has an upward slope

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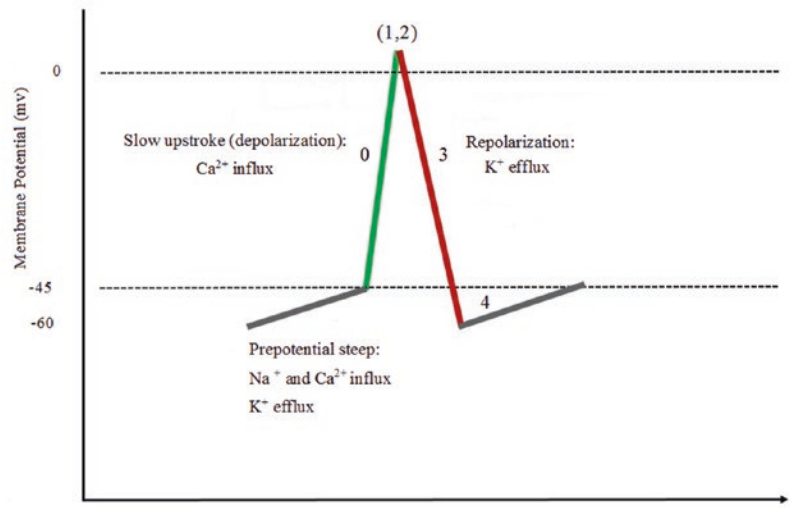

Fig. 4 Action potential (AP) in cardiac pacemaker cells. (Modified from Dabbagh A., et al. "Cardiac physiology"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management". Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp 65-116. Published with kind permission of © SpringerNature, 2017. All Rights Reserved)

dial cells and that is the "**refractory period**" which is the time interval during which there is no response to a new impulse or the response could be sluggish: ***absolute*** refractory period or ***relative*** refractory period, respectively. Though described as one of the basic properties of currents alongside the cell membrane, some studies strongly believe that post-repolarization refractoriness plays a protective role against "***reentrant***" mechanisms of arrhythmias, especially in preventing atrial fibrillation.

In all cells having a refractory period, the time interval for refractoriness is proportional to the time duration of action potential and it is primarily dependent on the duration of Phase 2 "***plateau***"; so:

- In atrial cells, the refractory period is usually shorter (about 0.15 s)
- In ventricular cells, it is about 0.25–0.3 s
- In pacemaker cells, the refractory period is about 0.3 s; while the refractory period

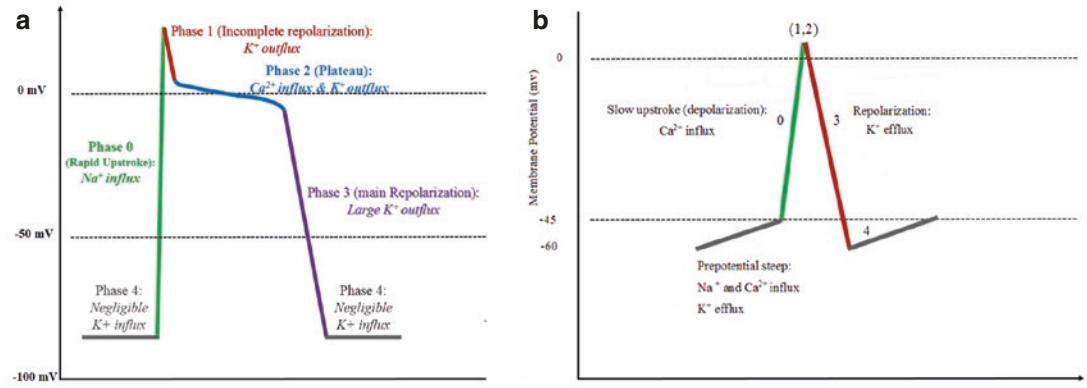

Fig. 5 The difference between Action Potential Phases in Normal (**a**) and Pacemaker (**b**) Cells. (Modified from Dabbagh A., et al. "Cardiac physiology"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management". Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp 65-116. Published with kind permission of © SpringerNature, 2017. All Rights Reserved)

continues up to the middle of the prepotential steep phase (Veenhuyzen et al. 2004; Coronel et al. 2012; Aziz et al. 2018; Joukar 2021; Kim et al. 2021).

What is the underlying mechanism for the automaticity of pacemaker cells? Three theories are proposed: ***M-clock*** theory, ***Ca^{2+} clock*** theory, and ***coupled clock*** theory, described here in brief:

M-clock theory: this theory, known as membrane clock (or just briefly ***M clock***), implicates that ion channels and ion transporters located on the myocardial cell membrane, their inward and outward currents, and their associated channels (i.e., mainly L-type Ca^{2+} channels, K^+ outflux channels, Na^+/Ca^{2+} exchanger "***NCX,***" Na^+/K^+ ATPase and funny currents) are the main generators of action potentials needed for pacemaker activity; this theory involves mainly the role of sarcolemma-related structures.

Ca^{2+} clock theory: this theory implies that Ca^{2+} is restored in the sarcoplasmic reticulum, the related Ca^{2+} pumps (Sarcoplasmic/endoplasmic Ca^{2+} ATPase: "***SERCA***"), Ca^{2+} channels including ryanodine receptor family (***RYRs***), and some members of the protein kinase family oscillate rhythmically and periodically to produce the pacemaker automaticity.

Coupled clock theory**:** though none of the two above theories are frankly dominant over the other theories, both cooperate to produce the pacemaker function in the heart having an important role in impulse generation; however, their cooperation with other proteins like protein kinase A (PKA) or Ca^{2+}/calmodulin dependent protein kinase II (CaMK II) is the basis for the model known as "***coupled clock theory***" being the most recent proposed theory for impulse generation and automaticity in the heart, especially in SA node; this theory implicates the wide interactions between cell membrane related mechanisms and intracellular mechanisms leading to impulse generation (Maltsev et al. 2006, 2014; Sobie et al. 2006; Maltsev and Lakatta 2007, 2012; Mangoni and Nargeot 2008; Lakatta et al. 2010; Yaniv et al. 2012, 2015; Hennis et al. 2021; Kim et al. 2021; Li et al. 2021).

Excitation-Contraction Coupling: ECC

ECC is the "linkage" phenomenon that translates the electrical activities of the heart to mechanical

activities; hence, it is the "***electromechanical interface.***" Nearly 50 years ago, this concept was proposed and since then, a great bulk of research has been done on this topic (Quinn et al. 2014). The terminal and eventual goal in ECC is the process of Ca2+ cycling leading to rhythmic initiation and termination of myocardial contraction. ECC has three main parts:

1. Ca^{2+}.
2. Functioning organelles of ECC.
3. ECC modulating mechanisms.

Calcium homeostasis should be discussed at first; since Ca^{2+} homeostasis has a central role in ECC. However, Ca^{2+} homeostasis is one of the most important cellular processes in all cells including myocardial cells. Intracellular Ca^{2+} is not only a second messenger, but in myocytes, it has other roles; the ***dual-phase pattern of Ca^{2+} cycling*** (i.e., Ca^{2+} release and Ca^{2+} reuptake) is the basis for lifelong contraction and relaxation of the heart; needless to say, many intracellular proteins are involved in Ca^{2+} homeostasis; on the other hand, many intracellular interactions of the heart are dependent on Ca^{2+} homeostasis, including:

- electrical function (with Ca^{2+} influx and efflux as integral parts of action potential),
- mechanical activities (with Ca^{2+} surge in systole and Ca^{2+} reuptake in diastole),
- cell energetics, especially inside the mitochondria,
- the buffering capacity of the cells for stress control,
- apoptosis and cell death dependent mechanisms.

Sarcoplasmic reticulum (SR) is the main source of intracellular Ca^{2+} storage; however, in the "pediatric heart" the amount of Ca^{2+} in SR is not as abundant as the SR of the adult heart; so, the myocardium of neonates, infants, and children is highly dependent on extracellular levels of Ca^{2+} for functioning normally, especially when because the calcium transport system in the myocardium of infants and children is immature. These unique features of Ca^{2+} homeostasis in the pediatric heart are among the main causes of reduced myocardial contractile force in this age group compared to the normal healthy adult (Bers 2002; Maier et al. 2005; Gustafsson and Gottlieb 2009; Asp et al. 2013).

The excitation-contraction coupling (ECC) involves several ongoing and interrelated events to act as a machine to promote cardiac function. The following steps occurring in a sequential cascade constitute the ECC (Tables 3 and 4):

Table 3 A summary of ECC

	Event	Protein or channel in-charge	The main phenomenon	Result
1	Initial Ca^{2+} influx (Ca^{2+} entry to the cell)	I_{CaL} DHPR	DHPR channel opens	Triggers CICR (opening of RyR-2)
2	Ca^{2+} release (CICR) due to opening of RyR-2	RyR-2	Channel opens and huge Ca^{2+} is released from SR	Starts myocardial contraction
3	Ca^{2+} recycling, from cytosol back to SR, i.e., Ca^{2+} reuptake and Ca^{2+} efflux	SERCA2a (mainly) and NCX	Recollection of Ca^{2+} from the cytosol	Starts myocardial relaxation
4	Modulation of SERCA2a	Phospholamban (PLB)	Stopping Ca^{2+} reuptake by SERCA2a	Stops myocardial relaxation; the next contraction could now start

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Table 4 A summary of the composing aspects of ECC and their related items

1	Functioning organelles of ECC	Cell membrane
		Thick and thin filaments
		T tubules
		Sarcoplasmic reticulum
2	Calcium ion (Ca^{2+})	Ca^{2+} influx to the cardiomyocytes (by L type Ca^{2+} channels in *systole*)
		Ca^{2+} release inside the cell (by RyR in systole)
		Ca^{2+} efflux from the cardiomyocytes (by NCX in diastole)
		Ca^{2+} reuptake from the cell (by SERCA in diastole)
3	Controllers of ECC	Ryanodine Receptor (RyR) family
		Dihydropyridine Receptor (DHPR)
		Calmodulin

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1. $\boldsymbol{I_{CaL}}$ or dihydropyridine receptor (DHPR) opens for initial primary Ca^{2+} influx; (Ca^{2+} trigger) from extracellular fluid (ECF)
2. The primary "***Ca^{2+} trigger***" causes the release of huge Ca^{2+} amounts from the junctional sarcoplasmic reticulum through ryanodine receptor-2 and other intracellular calcium reservoirs; these small primary amounts of Ca^{2+} spark the release of next huge amounts of Ca^{2+}; this phenomenon is called ***Calcium Induced Calcium Release*** (CICR); among many interesting features of CICR is that in some pathologies, CICR instability contributes to cardiac arrhythmias (Fabiato and Fabiato 1977, 1978; Fabiato 1983; Bers 2002)
3. CIRC causes huge Ca^{2+} release; then, Ca^{2+} interacts with contractile elements of the myocardial cells, starting the myocardial contraction
4. Immediately afterward, Ca^{2+} recycling, from cytosol back to the sarcoplasmic reticulum (SR) happens; this process is the main mechanism for Ca^{2+} reuptake and is done mainly by an ATP-dependent protein called sarcoendoplasmic reticulum Ca^{2+} transport ATPase (abbreviated as SERCA) functioning as a pump to recollect Ca^{2+}; more than 10 isoforms of SERCA have been recognized in different tissues; however, the primary isoform recognized in myocardial cells is SERCA2a; however, SERCA2a activity is not limitless and is modulated by another protein called phospholamban (PLB); PLB blocks SERCA2a through biochemical and structural transitions of its molecule (Sobie et al. 2006; Williams et al. 2010).
5. Besides SERCA2a, the remainder of Ca^{2+} is returned to ECF by NCX

So, these three main proteins interact together in the handling of Ca^{2+} homeostasis:

(a) ***First***: SERCA2a mediates Ca^{2+} reuptake and starts myocardial relaxation; in ***diastolic dysfunction***, SERCA2a is one of the most important therapeutic targets which is the goal for novel therapies aimed to augment SERCA2a or phosphorylation of PLB (i.e., inactivation of PLB; also see next paragraph); (Shareef et al. 2014). In one study, Pavlovic et al. demonstrated that the "PLB/SERCA ratio was significantly reduced in atrial myocardial tissue of pediatric patients with volume overload" (Pavlovic et al. 2005).

(b) ***Second***: PLB modulates SERCA2a activity, so stops myocardial relaxation and indirectly, stops diastole; also, PLB determines cardiac response to beta-1 adrenergic stimulation. When the cardiac muscle is stimulated through the β-1 receptor, increased cAMP ensues leading to increased activity of protein kinase A (PKA); increased phosphorylation of PLB on serine-16 as the result of increased PKA activity results in relieving PLB inhibitory effect on SERCA2a activity; the outcome of this story is increased Ca^{2+} pumping to SR and accelerated reuptake of Ca^{2+} from cytosol; the physiologic picture of this cascade would be speeding up the myocardial relaxation and shortening diastole; augmented PLB phosphorylation could a potential future therapy for diastolic dysfunction (Frank et al. 2003; Asp et al. 2013; Espinoza-Fonseca et al. 2015)

(c) ***Third***: Sarcolipin (SLN) is another cytosol protein that regulates Ca^{2+} homeostasis mainly in atrial myocytes somewhat similar to PLB in ventricular myocytes; though SLN and PLB are not the same regarding their structure, function, and anatomic site of action, their final function is to inhibit SERCA2a activity to terminate SERCA2a role in Ca^{2+} reuptake; decreased SLN in atrial myocytes is associated with the augmented activity of SERCA2a in atrial myocytes and SR Ca^{2+} overload which is associated with atrial fibrillation and atrial remodeling (Bhupathy et al. 2007; Periasamy et al. 2008; Xie et al. 2012)

- There are some congenital heart diseases titled under "conotruncal defects" resulting from altered neural crest migration and include Tetralogy of Fallot (TOF), transposition of great arteries, persistent truncus arteriosus, double outlet right ventricle, interrupted aortic arch, and other anomalies of aortic arch; in these congenital cardiac anomalies, neural crest impairment leads to important defects in SR, especially impaired RYR-2, impaired ECC, and defective $\boldsymbol{I}_{CaL}$; also, in some of these anomalies (mainly in TOF), impaired function of PLB and SLN is seen as a prominent defect in myocardial cytosol (Vittorini et al. 2007)
- Other proteins like calmodulin (***Cal***cium ***mod***ulated prote***in***) and calsequestrin are discussed here.
- There is another protein named calmodulin-dependent protein kinase II (CaMK II) which also could control and modulate SERCA2a (i.e., somewhat similar to PLB)

Functioning organelles of ECC are cell membrane; thick and thin filaments; T tubules; and sarcoplasmic reticulum:

1. The myocardial cell membrane or sarcolemma is the main player for both parts of ECC, that is, the electrical phase of ECC (which includes the creation of different phases of action potential) and the mechanical phase of ECC (which is primarily through Ca^{2+} trigger).
2. Thick and thin filaments.
3. Transverse tubules (T tubules).
4. Sarcoplasmic reticulum (SR): being divided into longitudinal SR (LSR) and junctional SR (JSR), acts as the main intracellular Ca^{2+} reservoir. SR releases and reuptakes Ca^{2+} per needed into and out of the cytosol; meanwhile, RyR-2 and SERCA are the main Ca^{2+} releasing and reuptake pumps located on JSR, respectively.

ECC modulating mechanisms: Some modulators balance the different interactions in ECC (Yang et al. 2011; Asghari et al. 2014; Brunet et al. 2015; Motloch et al. 2016):

- PKC modulates ECC.
- All types of VGCC, Ca(v)1.2, mediate ECC.
- There are some uncoupling proteins (UCPs), mainly located in the inner membrane of cardiac mitochondria; they belong to a superfamily of mitochondrial ion transporters and they modulate intracellular Ca2+; so, they modulate ECC by modulating mitochondrial Ca2+ uptake.
- The micro-architecture of the myocardial tissue has many aspects which have modulating role on ECC which are under further assessments

Mechanical (Contractile) Function of the Myocardium

The contractile function of the myocardium is the specific duty performed by two syncytia: ***atrial*** and ***ventricular***. These two syncytia are composed of a huge number of units called a sarcomere. Each sarcomere is defined as a specialized part of the myocardial muscle cell located

Table 5 Categories of myocardial filaments

	Contractile proteins	Modulatory proteins
Thick filament	Myosin Titin	Myosin-binding protein C (MBPC)
Thin filament	Actin	Tropomyosin Troponin (TnC, TnT, TnI) Tropomodulin

between two Z lines; the main ingredients of sarcomere are (Table 5):

Contractile proteins which are responsible for cardiomyocytes contraction (actin and myosin) and the backbone (such as titin); these proteins are arranged in a delicate structure between two Z lines and are discussed later

Regulatory proteins control the cyclic contraction-relaxation phases and are mainly troponin, tropomyosin, tropomodulin, and myosin-binding protein C, which activate and modulate sarcomere functions. The contractile elements of the cardiomyocytes could be divided as follows:

Inside each sarcomere, actin and myosin interactions lead to "Ca^{2+} triggered cross bridges" between actin and myosin leading to contraction; this contraction is the 3rd stage after electrochemical action-potential translated via the "ECC" pathway to contraction; so, the more cross bridges, the more contractile force. After each contraction, troponin I (TnI) detaches actin and myosin from each other; hence cross bridge sites (active sites) are disappeared. Cross bridges need great amounts of fuel supplied as sarcomere ATP reservoirs; both attachment and separation of cross-bridges are energy-consuming. This is the basis for cardiac systolic contraction and diastolic relaxation.

Although there are many similarities in the function and structure of the contractile tissue between a healthy adult heart and the pediatric heart, we should always keep in mind that the texture of the myocardium in the pediatric heart is organized in such a way that only about 50% of the tissue is composed of contractile elements; while the rest 50% of the tissue is composed of non-contractile elements, including mitochondria and large nuclei. This unique structural feature has some specificities:

- In the pediatric myocardium, the percentage of contractile mass in the total mass of the myocardium is less than in the adult myocardium; on the other hand, decreased contractile mass leads to decreased compliance of the ventricular muscle (compared to the adult healthy heart); this is one of the main reasons why the myocardial contractile reserve is significantly reduced compared to the healthy adult myocardium.
- Due to decreased compliance of the LV, the filling pressures (compared with adult healthy myocardium) are higher and preload augmentation is limited to just 1–7 mmHg.
- The neonatal myocardium is hence highly dependent on the resting tone of β adrenergic stimulation; in clinical practice, we see very high sensitivity of the neonatal myocardium to even low doses of β blockers and on the other side, the response to β agonists is not so much exaggerated as adult healthy myocardium.

Here, we first describe the main ingredients of each sarcomere, then we will describe their assembly including Z disc (Z line), M band, I band, and A band, and how thin and thick filaments are integrated into the framework of these structures in the sarcomere.

Thick filament is composed mainly of two contractile proteins (myosin and titin) and one modulatory protein (myosin-binding protein C or briefly MBPC).

Myosin has a structured framework. First of all, the 15-nanometer myosin rods are composed of the following elements:

- One myosin heavy chain (1 MHC).
- Two myosin light chains (2 MLCs).

Then, 1 MHC plus 2 MLCs compose a single myosin strand (MS); so, we will have:

1 MHC + 2 MLC's = MS

Afterward, two MS has woven together to produce one myosin molecule (MM); in other words, each MM is composed of two MSs:

1 MM = 2 MS = 2 MHC's + 4 MLC's

However, each MM resembles a "golf club" which has two functional domains: the four MLCs in the ***head region*** and the ***tail region*** of the MM which is like the handle of the golf club (Fig. 1). Ca^{2+} trigger causes the head of MM to cross bridge with actin leading contractions. Also, TnI inhibits the cross-bridges at the end of each interaction to detach actin from the myosin head.

About 300 MMs collect together in a parallel fashion, forming myosin rod (MR) which resembles "***a bundle of golf clubs***" collected together, while their heads protrude out of the bundle and their bodies and handles are attached (Fig. 6).

Titin is the most frequent filament after actin and myosin. Titin is a very giant filament extending from each side of the Z line towards the M line: "***the largest protein known to date***"; it has been simply named the "***bidirectional molecular spring***" of the cardiac sarcomere; in other words, during diastole, the extensible properties of titin help myocardial tissue to preserve its primary configuration, returning to the primary size of the heart; in this way, titin acts as a "***passive force generator***" in diastole; on the other hand, titin plays its role in the restoration of sarcomere length when it is shorter than its slack length. Besides, titin has attachments with actin-myosin cross-bridge sites through the myosin-binding protein C (MBPC). This is why titin has a very strategic role in cardiac sarcomere to keep it stable during contraction and relaxation (Pyle and Solaro 2004; Solaro 2005; Kobirumaki-Shimozawa et al. 2014).

Titin has a specific structure that helps create its elastic role. Functionally speaking, titin has two segments:

- The extensible segment anchored to each side of the Z line located in the I band domain; this is the N terminal of titin.
- The nonextensible segment located in the A band; the end of the C terminal is bound to the thick filament.

On the other hand, if we want to explain titin based on a structural classification of the molecule, it has two parts:

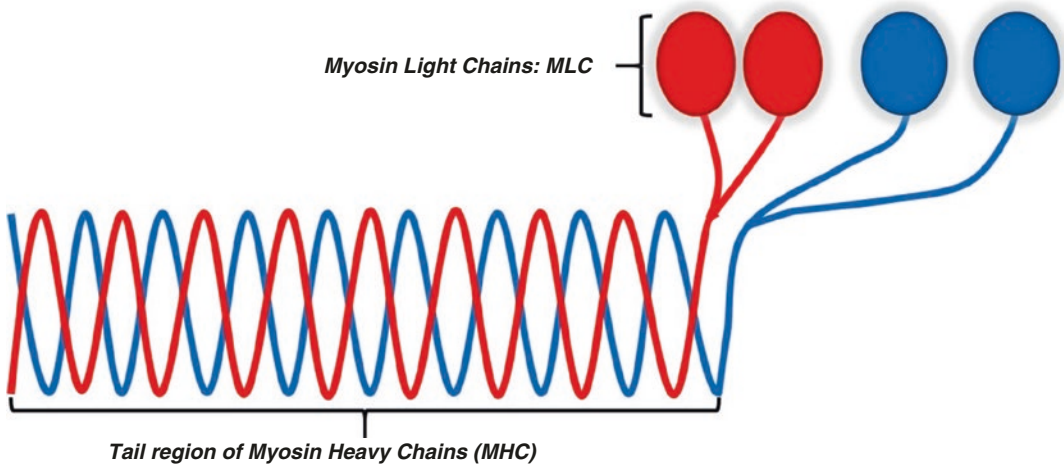

Fig. 6 Schematic presentation of a myosin molecule. (Modified from Dabbagh A., et al. "Cardiac physiology"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management." Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp 65-116. Published with kind permission of © SpringerNature, 2017. All Rights Reserved)

- Immunoglobulin-like segment.
- PEVK segment is abbreviated for the four amino acids: Proline (P), Glutamate (E), Valine (V), and Lysine (K); these amino acids comprise about 75% of the PEVK segment.

The role of titin in "***fine-tune passive myocardial stiffness***" and "***diastolic function and diastolic force generation***" is highly dependent on phosphorylation of titin molecule by calcium/calmodulin-dependent protein kinase II delta (CaMKIIδ); those regions of titin located in "I band" are important in phosphorylation mechanisms. Impairment in CaMKII-dependent phosphorylation of titin is considered a major etiology for diastolic dysfunction. Mutations in those genes related to titin are often considered the etiologic factor for dilated cardiomyopathy (DCM); since titin, disruption ends in impairment of the structure of the heart and its elasticity (LeWinter et al. 2007; Nishikawa et al. 2012; Hamdani et al. 2013a, b; Hidalgo et al. 2013; Kotter et al. 2013; Rain et al. 2014; McNally et al. 2015; Zile et al. 2015)

Titin stiffness could lead to RV diastolic dysfunction in pulmonary hypertension patients, of course in association with factors like reduced phosphorylation of cTnI and altered phosphorylation of Ca^{2+} (Rain et al. 2014).

Also, in heart failure patients, impaired phosphorylation of the thick filament protein myosin-binding protein C (cMyBP-C) has a main role especially in patients with the diagnosis of familial hypertrophic cardiomyopathy (HCM) due to mutations in MYBPC3 (Kuster et al. 2012).

The **thin filament** is composed of actin (mainly in form of filamentous actin "***F actin***"), tropomyosin (TM), and troponin complex (Tc); if we want to compare the number of molecules for each protein in the thin filament, then we will have one F actin, two TM, and two Tc in each imaginary unit of the thin filament.

Actin: actin is made of F actin; so, F actin is the backbone of the thin filament, while TM is located in the groove of the F actin strand; however, Tc is located at defined and regular intervals along F actin. Each molecule of F actin is composed of 13 subunits called globular actin "***G actin,***" which twist to form a 360 degrees turn in the F actin strand. In cardiac sarcomere, F actin is the alpha subtype.

Tropomyosin (TM): tropomyosin is a ***right-handed helical coiled-coil*** and inhibitory protein located on F actin. Two adjacent TM molecules attach and turn round each other; then, this coiled filament (composed of two turned TM molecules) twists once more while being attached to the actin filament; so, the term "the prototype coiled-coil" protein. Each TM molecule is in contact with seven subsequent G actin molecules; so their molecular ratio is "Tm 1: G actin 7." The end of one TM molecule is attached to the head of the next TM molecule; this attachment, called head-to-tail overlap of TM, has about eight amino acids. This head-to-tail interaction of each two subsequent TM molecules is of the most determining factors modulating the function of the thin filament. Of course, recent studies have demonstrated that this description is somewhat a simplified picture of the real structure of TM (Kobayashi et al. 2008; Nevzorov and Levitsky 2011).

TM is under the control of two parts of the troponin complex: troponin T (TnT) and troponin I (TnI); in cardiac muscle, Ca^{2+} attachment to troponin C (TnC) causes TM to be detached from the actin-myosin cross-bridge site; this is exactly the point which is inhibited by TM; in other words, Ca^{2+} inhibits TM, then, this "inhibition," exposes the "cross-bridge site" to myosin molecule; this is exactly the myosin-binding site on actin molecule known as ***cross-bridge site*** or active site***;*** in this process, when TM is pushed far from cross-bridge sites, myosin cross-bridge finds the opportunity to directly attach to this critical point, that is, the cross-bridge; and these interactions lead to sarcomere contraction. At the end of the contraction, when Ca^{2+} concentration in sarcomere falls, troponin I (TnI) augments the role of TM; in such a way that again TM becomes closer to cross bridge sites, attaches to cross the bridge, and pushes myosin away from cross bridge; the outcome is inhibition of contraction. In this process, the two most important modulators for the sensitivity of sarcomere filaments to Ca^{2+} are the sarcomere length (i.e., Frank-Starling

relationship) and the role of protein phosphorylation in sarcomere which causes posttranslational modification of these proteins; the reader can find a detailed discussion in some reviews published in the last years (Hitchcock-DeGregori 2008; Kobayashi et al. 2008; Jagatheesan et al. 2010; Bai et al. 2013).

There are two specific inherited diseases involving the impaired function of TM in Ca^{2+} attachment: dilated cardiomyopathy (DCM) and hypertrophic cardiomyopathy (HCM); both are due to "missense mutations" in genes coding TM. In summary, in DCM, the mutation causes decreased sensitivity of TM to Ca^{2+} binding, while in HCM, the mutation ends in increased sensitivity of TM to Ca^{2+} (Bai et al. 2013; Redwood and Robinson 2013; Kalyva et al. 2014) (Fig. 7).

Troponin complex (Tn): troponin complex is composed of three subsegments: troponin C (TnC), troponin I (TnI), and troponin T (TnT); TnI inhibits the cross-bridge by inhibiting the actin-myosin-TM interactions, while TnC activates muscle contraction by "***inhibiting the inhibitory role of TnI***"; TnT is the modulator for troponin activity. The troponin complex is not just a simple attachment of three proteins; instead, the conformational interactions between these three components are mandatory for the activity of the troponin complex.

Troponin C (TnC): this protein acts as a "Ca^{2+} sensor" that senses and regulates the sequential events involved in the initiation and control of contraction inside the sarcomere. The shape of TnC is much similar to a dumbbell; two heads of the dumbbell are the N terminus and the C terminus of the TnC molecule.

There are two Ca^{2+} binding sites (CBS) on the C terminus (CBS III and CBS IV); Ca^{2+} is attached firmly to both of them; so none of them is involved in controlling Ca^{2+} dependent muscular contractions; however, these two Ca^{2+} binding sites (i.e., CBS III and IV) are attached to TnC and TnI. On the other hand, there are two other Ca^{2+} binding sites on the N terminus of TnC: CBS I and CBS II; however, CBS I cannot attach to Ca^{2+} firmly; while ***CBS II*** is the only and most important CBS that attaches to Ca^{2+} and performs the regulatory and modification roles of TnC in muscle contraction. Attachment of Ca^{2+} to CBS II on the N terminus of TnC causes structural and functional changes in both the "actin-TM" complex and the troponin complex; these changes cause activation of the thin filament. TnC mutations are involved in both HCM and DCM (Marston and Redwood 2003; Kobayashi et al.

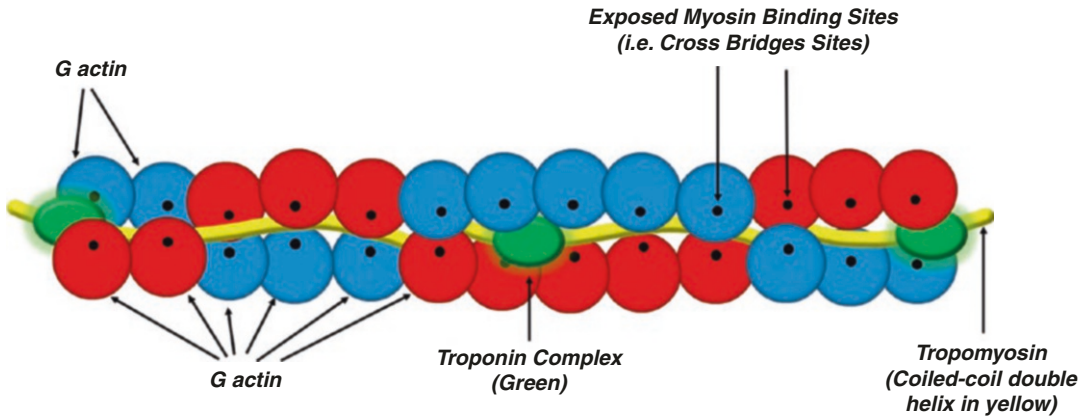

Fig. 7 Schematic presentation of a thin filament (also see Fig. 8a): each helix of F actin contains 2 strands of G actin each containing 13 G actin molecules (blue and red globes), myosin-binding sites which expose actin for cross bridging with myosin and located on each G actin (demonstrated as a black dot); troponin complex (Green knobs) and Tropomyosin double-strand coiled coils as yellow threads). (Modified from Dabbagh A., et al. "Cardiac physiology"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management." Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp 65-116. Published with kind permission of © SpringerNature, 2017. All Rights Reserved)

2008; Kekenes-Huskey et al. 2012; Craig et al. 2014; Kalyva et al. 2014; Kobirumaki-Shimozawa et al. 2014; Shi et al. 2015).

Troponin I (TnI): this part of troponin has an inhibitory role; not only does TnI alone inhibit actin but also, when combined with TM, the TnI-TM complex acts as a potent inhibitor of actin-myosin interaction and so, prevents the generation of forceful contractions. Some genetic disorders in TnI cause hypertrophic cardiomyopathy (HCM) or restrictive cardiomyopathy (RCM) because of impairment in inhibitory effects of TnI in diastole. The interested reader is addressed to detailed references for TnI (Chang et al. 2008; Kobayashi et al. 2008; Ohtsuki and Morimoto 2008; Solaro et al. 2008, 2013).

Troponin T (TnT): TnT is an integrating component of the thin filament and connects TM to the troponin complex. TnT attaches to the "head-to-tail" segment of two subsequent TM segments on one hand and the Z disc on the other hand; this protein has a cooperative role in thin filament activation through its modulatory role on TM activity. To explain more, the inhibition of TnI would be relieved without any need for Ca^{2+} if there was no TnT; but in the presence of TnT, Ca^{2+} is mandatory for TnC activity to lift the inhibitory role of TnI. TnT is composed of two subfragments: TnT1 (N terminal) and TnT2 (C terminal): TnT1 binds strongly to tropomyosin, while TnT2 has an important role in Ca^{2+} regulation; the function of TnT on Ca^{2+} regulation would be impaired without TnT2. The majority of the mutations leading to DCM are related to TnT, though TnI and TnC also have mutations leading to DCM. Also, some mutations in TnT lead to HCM (Chang et al. 2008; Kobayashi et al. 2008; Ohtsuki and Morimoto 2008).

A main functional part of interactions between these proteins is the cross bridging phenomenon, a basic phenomenon with its integral role in myocardial contraction; which is based on continuous interactions between the thick and thin filaments.

Z disc, I band, A band, and M line (the following components are demonstrated in Fig. 8a, b): Sarcomeres are cylindrical repeating units; the margin of each sarcomere is Z disc or Z line.

Z in Z discs stands for Zuckung, a German name meaning twitch; Z discs are thee-dimensional structures about 100 nm (0.1 μ) composing the margins of each sarcomere; in fact, Z discs are the border of two neighboring sarcomeres and they divide the sarcomeres from each other. However, each Z disc is a complex of many proteins including those located at the Z disc and those attached to the Z disc.

Functionally, Z discs have the main following roles:

- Producing mechanical stability in each contraction and relaxation; since Z discs are the anchoring site of many sarcomere proteins and also, the anchoring site for thin filament and titin.
- Transmission and transduction of signal between two adjacent sarcomeres.

Each Z disc is surrounded on each side by the **I band**; which is the dark band adjacent to the Z disc; each I band spans thin filaments of the two adjacent sarcomeres with the Z disc located in its center.

There is a pivotal band for the thick filaments called the **M band**; these bands are in the **M**iddle of the sarcomere, so the **M** band. *Both Z discs and M bands are transversally oriented multi-protein scaffolds (*Stehle et al. 2009*).* On either side of each M band, thick filaments compose the "**A band.**" A band is a band on each side of the M band which is the region of thick filaments; the lateral border of the A band contains the terminal segment of the thin filaments which together with thick filaments slide into each other during contraction and come out during relaxation (Tskhovrebova and Trinick 2010).

One A band in the middle plus two "half I bands" on each side compose the span of one sarcomere which is between two Z discs.

On the other side, the specific segment of the A band located in the center of the A band which

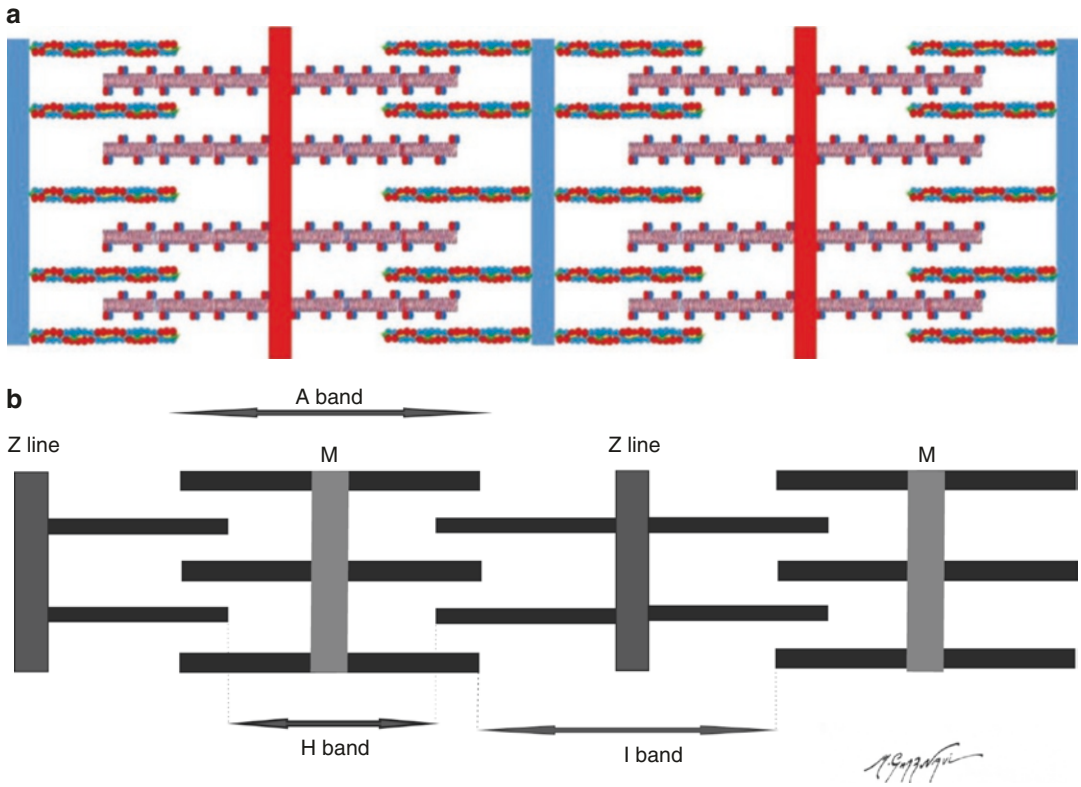

Fig. 8 (**a**) Schematic presentation of the microscopic structure of a sarcomere from a wide view (also, see Fig. 7). (**b**) Schematic presentation of the microscopic structure of a sarcomere (compare each part with its compared part in Section A). (Figure **b** is modified from Dabbagh A. "Cardiac physiology"; in "Postoperative Critical Care for Cardiac Surgical Patients". Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp 1-39. Published with kind permission of © Springer, 2014. All Rights Reserved)

is devoid of thin filaments is called the "**H band**" (Solaro 2005; Kobayashi et al. 2008).

In summary, the attachment of filaments of sarcomeres is as follows (Stehle et al. 2009):

- **Thick filaments** are anchored just at their midpoint to the M-line; then, each thick filament spans in each of the two lateral sides towards the Z-discs; however, it does not attach to Z disc.
- **Thin filaments** are attached and anchored to Z-lines and extend from the Z line towards the midpoint of the sarcomere; that is, the M-line; again, thin filaments do not attach to the M line.
- **Titin**, the huge protein of the thick filament, is attached on one side to the Z disc and on the other side to the M band; so, titin is spread ***all along the sarcomere*** from the Z-disk on one hand to the M-band of the sarcomere on the other hand; Also, there is alpha-actinin, a specific protein located in Z line, connecting thin filament with titin (Anderson and Granzier 2012).

Novel Therapeutic Agents Against Heart Failure

Based on the protein molecules and the protein architecture involved in myocardial contraction, a wide array of novel therapeutic agents are under assay which is briefed here:

Omecamtiv mecarbil, a ***myosin activator*** agent, enables myosin to be attached much more "firmly" to actin to produce more forceful myocardial contraction; this drug acts directly on sarcomere, without any perturbation in myocardial Ca^{2+} homeostasis inside the cell; omecamtiv mecarbil increases the rate of actin-dependent release of phosphate, resulting in increased actin-attached myosin heads, causing an increased number of active, force-generating myosin heads during systole and also, increased effectiveness of myosin cross-bridge formation and duration; so, systolic ejection time increases without any unwanted effects on left ventricular filling pressure or any unwanted increase in myocardial contraction velocity; the drug seems to be a good pharmacologic agent for systolic heart failure; however, it is not yet available for clinical use (Cleland et al. 2011; Malik and Morgan 2011; Teerlink et al. 2011; Aronson and Krum 2012; Garg and Frishman 2013).

Istaroxime has a dual function; first, it inhibits sarcolemmal Na+/K+ ATPase to increase intracellular Na+ concentration and decrease Ca^{2+} efflux through NCX; so, increasing intracellular Ca^{2+} concentration; second, istaroxime stimulates SERCA2a to augment lusitropic properties of the myocardium and decrease the chance for arrhythmias; it also protects the heart through stabilization of SERCA2a (George et al. 2014; Ahmad et al. 2015).

In diastole, Ca^{2+} overload happens which is either due to decreased rate of Ca^{2+} reuptake or increased sensitivity of the myocardium to Ca^{2+}. Novel therapies have been proposed to treat diastolic dysfunction through augmentation of SERCA2a or partial inhibition of PLB (Kawase and Hajjar 2008; Teerlink et al. 2009; Kawamura et al. 2010; Asp et al. 2013).

Control Mechanisms of Cardiac Function

Autonomic Control of the Heart

The autonomic nervous system (ANS) as a portion of the peripheral nervous system continuously controls cardiovascular functions.

The ANS, on the other hand, is regulated by other centers such as the brain stem and hypothalamus. The sympathetic and parasympathetic systems are the main component of ANS.

The preganglionic nerves of the sympathetic system originate from the T1-L2 segment of the spinal cord and enter sympathetic chain ganglia located along the side of the viscera column (i.e., paravertebral ganglia). Postganglionic fibers of the cardiac sympathetic originate from the stellate ganglia and extend to different parts of the heart (SA and AV nodes, atria, and ventricles).

The long preganglionic nerves of the cardiac parasympathetic system originate in the dorsal motor nucleus of the 10th cranial nerves (left and right vagi) or the nucleus ambiguous. The short postganglionic nerves lie on the epicardial surface and within the atrial and ventricular walls. There is no equal vagi distribution to different cardiac structures because the vagi mainly affect SA and AV nodes and there is a slight distribution for atria and ventricles.

In the newborn heart, the number of α -adrenergic receptors is reduced; this is among the factors that limit the function of the left ventricle; also, the level of the circulating catecholamines increases dramatically to compensate for the limited function of the heart, an important fact that should be considered when anesthetizing a child or newborn, especially for cardiac procedures; it is logic to avoid suppressing the sympathetic tone of the body to prevent decreased cardiac output.

Since the right and left sides of the embryonic structures are the sites for developing the SA and AV nodes respectively, the SA node receives its ANS branches mainly from the right vagus and right stellate ganglion and the AV node takes its branches mostly from the left vagus and left stellate ganglion. Sympathetic β-receptors are epicardial and parasympathetic muscarinic receptors are endocardial (Gordan et al. 2015).

Sympathetic and Parasympathetic Receptors

There are different subtypes of α (α_{1A}, $\alpha_{1B,}$ and α_{1D}) and β ($\beta_1$and β_2) sympathetic (or adrenergic) receptors in the heart.

Although the number of α_1-receptors is less than β-receptors, activation of α_1-receptors leads to increase ventricular contraction, the sensitivity of contractile myofilaments to calcium ions, and cardiac hypertrophy. Activation of the α_1-receptor as a $G_{q/11}$-coupled receptor by stimulating phospholipase-C (PLC) leads to enhance in intracellular inositol triphosphate (IP3) and diacylglycerol (DAG) concentration.

The β1 adrenergic receptors are expressed in the different portions of the heart such as; the SA node, AV node, atrial and ventricular cardiomyocytes. The activation of β1 receptors increases heart rate and augments myocardial contractility by increasing the intracellular calcium concentrations through calcium currents from the extracellular fluid and the sarcoplasmic reticulum (SR) stores and enhances the AV node conduction velocity. The β1 adrenoceptor is a G_s-protein-coupled receptor and activation of α_s (as a subunit of G-protein) by stimulating adenylyl cyclase increases the cAMP production and raises protein kinase A (PKA) activity. Although the number of the β2 receptors subtype is less than the β1 receptor, the effects of both subtypes are similar to each other.

The M2 subtype of muscarinic receptors is the dominant receptor for the parasympathetic nervous system in the heart. This receptor is coupled to the Gi-protein and activation of α_i by inhibition of adenylyl cyclase reduces cAMP production and lessens PKA activity. In addition, the βγ portion of Gi-protein activates acetylcholine-sensitive potassium channels (I_{KAch}) and creates hyperpolarization (Thomas 2011).

Functions of the ANS in the Heart

The ANS has a prominent effect on the different features of the heart due to its capacity to modify heart rate (chronotropy), contractility (inotropy), conduction velocity (dromotropy), rate of relaxation (lusitropy), and degree of excitability (bathmotropy).

Chronotropy changes are created via changes in the steepness of pacemaker potential in the SA node; inotropy, regulated by modulation of myocardial force generation through different mechanisms; dromotropy, altered by changes in the speed of impulse conduction in the AV node; lusitropy, controlled by the manners that return heart muscle to its initial relaxed condition after each muscle contraction and bathmotropy, modified by changes in the threshold of heart excitation. The different effects of the $\beta_1$and M_2 receptors' activation on the heart have been summarized in Table 6 (Myslivecek and Trojan 2003).

Inotropic Effects of the β1 and M2 Receptors Activation

Intracellular rise of free Ca^{2+} concentration is a fundamental factor for initiating myocardial contraction and for this, two important Ca^{2+} sources play a part; (1) extracellular fluid (ECF); and (2) sarcoplasmic reticulum (SR). Nearly, 20% of needed Ca^{2+} is provided from ECF and the remaining (80%) from SR. During the plateau phase of the action potential, Ca^{2+} enters the muscle fiber from ECF via L-type Ca^{2+} channels for generating the great release of Ca^{2+} from the SR through the ryanodine channel in the CICR phenomenon described earlier in this chapter.

There are many reasons for the positive inotropic effect of β_1-adrenoceptor stimulation by released catecholamines from the postganglionic neuron of the sympathetic system (norepinephrine) and adrenal gland (epinephrine):

1. Increase in the PKA activity via phosphorylation of L-type Ca^{2+} channel leads to an increase in the Ca^{2+} influx
2. Increase in the Ca^{2+} influx leads to a greater release of Ca^{2+} from SR and this action reinforces the intracellular concentration of Ca^{2+}
3. Catecholamines provide further Ca^{2+} stores in the SR for the next contraction by the increase

Table 6 Myocardial receptors characterized by their properties

Receptor type	Inotropy	Chronotropy	Dromotropy	Lusitropy	Bathmotropy
β_1	+	+	+	+	+
M_2	–	–	–	–	–

in activity of SERCA and further Ca^{2+} pumping into the SR at the end of the previous contraction. In addition, enhanced Ca^{2+} influx through L-type Ca^{2+} channels leads to an increase in Ca^{2+} availability for more storage in the SR
4. Sensitivity of troponin-C for Ca^{2+} is increased and this action facilitates the sliding of actin and myosin filaments for contraction achievement

As mentioned earlier, stimulation of the vagus nerve has a slight direct effect on myocardial contractility due to poor distribution of parasympathetic on the atria and ventricles. On the other hand, severe stimulation of the vagus nerve has a significant inhibitory effect on myocardial contractility mainly by reducing heart rate.

Chronotropic Effects of the β1 and M2 Receptors Activation

Activation of Gs-protein coupled β_1-adrenoceptor by pharmaceutical agents like epinephrine and norepinephrine enhances the heart rate through two mechanisms:

1. By increasing I_F (I_h) and I_{Ca} in the SA node which leads to an increase in steepness of pacemaker potential of action potential.
2. By increasing I_{Ca}, which causes a more negative threshold of the action potential.

Both of the above mechanisms accelerate the generation of the next action potential and shorten the interval between two consecutive action potentials.

On the other hand, contrary to β_1-adrenoceptor, activation of Gi-protein coupled M2 receptor by acetylcholine (Ach) slows the pacemaker activity of the SA node through three mechanisms, leading to decreased heart rate:

1. Acetylcholine decreases the steepness of pacemaker potential by reducing I_F and I_{Ca}.
2. Activated βγ portion of Gi-protein opens acetylcholine sensitive potassium channels (I_{KAch}) and increases outward potassium current; this effect produces "a hyperpolarization state" in the SA node.
3. Reduction in I_{Ca} changes the threshold of action potential to the more positive level.

All these three mechanisms decrease the speed of action potential generation, finally reducing heart rate (Chemla et al. 2000).

Lusitropic Effects of the β1 Receptor Activation

Catecholamines enhance cardiac relaxation by stimulation of β_1-adrenoceptor. After binding catecholamines to these receptors, Protein Kinase A (PKA) is activated. This activated enzyme can phosphorylate some proteins in the cardiomyocytes such as **phospholamban** which is a regulator of ion transport and a major substrate for PKA. Phospholamban reduces the uptake of Ca^{2+} into the sarcoplasmic reticulum by inhibiting SERCA and this effect creates a delay in starting myocardial relaxation after each contraction. Phosphorylation of phospholamban by PKA declines the inhibitory effect of phospholamban on SERCA and leads to an increase in the reuptake of Ca^{2+} into the SERCA (as described earlier in this chapter). Finally, reduction of intracellular Ca^{2+} level creates earlier relaxation.

Phosphorylation of the troponin I is another action of PKA to augment myocardial relaxation; this effect reduces the affinity of troponin C for Ca^{2+} binding and provides relaxation conditions for cardiomyocytes.

Developmental Changes in the Fetal Cardiac Contractile System

In this section, some developmental changes in the cardiovascular system are discussed. Of course, in the first sections of this chapter, **"evolutional transition in cardiac physiology"** is discussed in detail and is not repeated here.

Developmental Changes in Cardiac Ca^{2+} Homeostasis

1. Ca^{2+} homeostasis is not as fast in embryonic age as in the adult heart; however, it develops to increase its speed regarding Ca^{2+} transport after the mid-embryonic stage.
2. development of SERCA2a activity starts to develop during embryonic stages.
3. in embryonic and neonatal heart, mitochondrial Ca^{2+} transport is not as active as in adult cardiac cells.
4. Ca^{2+} transport through sarcolemma and SR of neonatal myocytes is immature; **this is mainly due to deficient or incomplete T-tubules and also, scant and small SR**; also, Ca^{2+} content of SR is not enough; as far as myocardial tissue development goes on, these structures develop and also, Ca^{2+} content increases to normal levels (Nakanishi et al. 1988; Wetzel et al. 1991; Mahony 1996). In clinical practice, two very important facts are seen:
   (a) Myocardial contractility in neonates and infants is highly dependent on extracellular Ca^{2+} stores; since intracellular Ca^{2+} stores are negligible.
   (b) Volatile anesthetics suppress myocardial contractility in neonates and children much more than in adults, a finding which supports immature SR and limited intracellular Ca^{2+} stores in this patient population; especially regarding the degree of maturity of NCX; however, some believe that Ca^{2+} influx channels - not immature SR- are the main mechanism responsible for the effects of volatile agents (Frank et al. 1994; Seckin et al. 2001; Prakash et al. 2002; Park et al. 2007).
5. CICR is not a dominant phenomenon in embryonic heart Ca^{2+} homeostasis; however, it develops as a cellular mechanism as far as the heart changes from an embryonic heart to a mature type of heart.
6. the compliance of the myocardium is less in neonates and infants than in older children and adults; in fact, ventricles in neonates and infants are stiffer and do not relax during diastole as much as adult ventricles; this stiffness in part is related to decreased concentration of SERCA2a, RyR, and NCX.
7. also, diastolic relaxation in the embryonic heart is not as fast as in the adult heart; this delay is not only due to decreased speed of Ca^{2+} kinetics in the cytosol, but also, due to incomplete development of diastole (Kawamura et al. 2010).
8. L type Ca^{2+} channels have a unique model for their development which dominates their role in the heart; so, as age increases, their developmental course changes, and improvement in their function happens (Qu et al. 2011).

Developmental Changes in Cardiac Action Potential

1. Resting membrane potential in neonates is less dependent on K^+ current; though this process changes with increasing age which develops to become as in the adult heart (Chen et al. 1991).

Developmental Changes in Mechanical Force Production and Contractile Function

1. The fetal heart has "**low specific force**"; as gestation goes on, the force production property of the heart increases and force development is augmented; also, the rate of force development and the rate of relaxation are both slow in the fetal heart; however, this rate increases as much as the embryonic heart develops (Marston and Redwood 2003; Schwan and Campbell 2015; Racca et al. 2016).
2. The myofibrils of the cardiac muscle elongate and also, their width increases as the age of the embryo increases.
3. M-line and Z-band are among the very early appearing structures of the cardiomyocyte; they are apparent about day 52 in the fetal period (Schwan and Campbell 2015; Racca et al. 2016).

4. β-myosin is among those structures and proteins which is seen so early in cardiac muscle cells (Marston and Redwood 2003).
5. Cardiac troponin I (TnI) increases progressively while at the same time slow skeletal TnI decreases (Sasse et al. 1993; Schwan and Campbell 2015).
6. All these changes during the gestation of the cardiac myocytes lead to improvements and development of the contractile function; so, these developmental changes are the basis for improved force production as the embryonic heart develops; however, the trend of maturation continues after birth, during childhood, and adolescence to lead to the final cardiac structure seen in the adult heart with the contractile properties of the adult heart.

Developmental Changes in Myocardial Function

The myocardium of an infant has a relatively fixed volume. The main reason is in the texture of an infant the myocardium has about 50% connective tissue with just the remaining 50% being contractile tissue. So, the reserve of the heart is really limited and the cardiac output in an infant is highly dependent on heart rate. If preload increases, there is not much significant difference in cardiac output due to limited cardiac tolerance for diastolic filling pressures: a small increase in diastolic volume load leads to a large increase in diastolic filling pressures. This is why the least amount of parasympathetic overactivity is poorly tolerated in a borderline heart of an infant with underlying cardiac disease. Also, the cardiovascular system of an infant keeps the increased heart rate up to 6 years old to compensate for this phenomenon.

Cardiac Cycle and Cardiac Work

Normal Cardiac Cycle

Cardiac pathologies cause different grades of impairment in the normal physiology of the heart; leading to altered cardiac work. So, we aim to move towards normal conditions as much as possible; it means that we want to have a heart, as much normal as possible with its pumping activity in an appropriate manner and also, with proper timing and force; in other words, our treatment goal is to make cardiac work as much as possible normal. For this purpose, in diseased hearts, we need the "***cardiac cycle***" to be as much as possible normal.

So, we should have normal function in the following items:

- ***Diastole***: with proper timing and normal filling pressures; over-pressurized chambers are in contradiction with normal work; a major part of normal diastole is having normal pressures in the pulmonary vasculature.
- ***Systole***: appropriate amount of blood with appropriate force and timing should be propelled out of the cardiac chambers in systole.

Systole and diastole are divided more into 4 stages which are organized one after another in a cycle called the cardiac cycle (Table 7):

1. Phase 1: "**Diastolic filling**" with "mitral and tricuspid" valves are open and "aortic and pulmonary" valves are closed; so, ventricular cavities gradually fill; the following forces are the main determinants of ventricular cavity filling in diastole:
   (a) Diastolic compliance of the ventricles is very low, especially in neonates and younger children.
   (b) The difference between the pressure in atrial and ventricular cavities (i.e., atrial-ventricular pressure gradient).
   (c) The atrial kick force (atrial contraction).
2. Phase 2: "**Isovolumic systole**": no change in volume of the ventricle; instead, continued rise in ventricular pressure; during the very early stages of this phase, the atrioventricular (AV) valves are closed; however, the aortic and pulmonary valves are opened just at the late milliseconds of this stage; that is, when intra-cavity pressure increases above a critical level; this is the start of the next phase.

Table 7 The sequence of phases in the normal cardiac cycle

	Name of the phase	Intra-cavitary pressure	Intra-cavitary volume	State of the valves
1	Diastolic filling	Gradually ↑	Gradually ↑	AV valves open; aortic and pulmonary closed
2	Isovolumic systole	Increases up to a critical level	No change:↔	AV valves are closed; aortic and pulmonary valves *just* open
3	Systolic ejection	Blood ejection causes a sudden drop	Suddenly decreases	AV valves are closed; aortic and pulmonary valves are completely open
4	Isovolumic relaxation	Gradually ↓	Starts filling	AV valves open; aortic and pulmonary valves closed

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3. Phase 3: "**Systolic ejection**": is accompanied by blood ejection from the left ventricle to the aorta and right ventricle to the pulmonary artery; the systemic and pulmonary vascular beds are perfused thereof; ventricles are emptied and decompressed after ejection.
4. Phase 4: "**Isovolumic relaxation**": both ventricles relax and their dimensions increase; due to the falling pressure of the ventricular cavity, the aortic and pulmonary valves are closed; meanwhile, due to the same reason, mitral and tricuspid valves open. Now, the cardiac cycle starts a new cycle from phase 1 and this goes on (Tanaka et al. 1993; Gibson and Francis 2003; Carlsson et al. 2012; Chatterjee 2012; Mitchell and Wang 2014).

Cardiac Work

Cardiac work: Cardiac work implies the product of myocardial performance and is the algebraic sum of two different items; first, the "***external work***" which is equivalent to the total myocardial energy used for ejecting blood out of the ventricles to the systemic and pulmonary vascular bed. The second parameter is the "***internal work***" which is the total energy needed by myocardial tissue to maintain cell energetic, myocardial integrity, and homeostasis of cardiomyocytes. For calculating the external work, we use the product of "*stroke work* multiplied by *ventricular cavity pressure.*" However, we usually calculate the external work by calculating the Area Under Curve of the pressure-volume loop of the left ventricle (i.e., LV pressure-volume AUC). The main myocardial need for energy reserve and its oxygen consumption is for used for external work; however, myocardial ischemia would jeopardize mainly the external work. There are some clinical indices for the assessment of cardiac work. Since we could not measure the cellular energy easily in clinical practice, we use some indices which are discussed here. These are stroke volume, cardiac output, and ejection fraction.

Stroke Volume: each "stroke volume" is the amount of blood ejected from the heart in each cardiac beat. Stroke volume (SV) is the result of "end-diastolic volume (EDV) minus end-systolic volume (ESV)" or simply, "SV = EDV – ESV." According to this equation, both EDV and ESV could affect SV. However, which factors could affect EDV and ESV?

1. EDV depends directly on two factors:
   (a) **Venous return** is the returned blood to the ventricles from veins; that is, from inferior and superior vena cava (IVC and SVC) to RV and from pulmonary veins to LV.
   (b) Diastolic time of ventricular filling or simply "**filling time**" which is the time in diastole that blood accumulates in ventricles; the longer the filling time, the more would be SV.
2. ESV depends on three factors:
   (a) **Preload** is the amount of ventricular stretching; the more stretch in the ventricle, the more contractile force; this is dis-

cussed more in the section of "Frank-Starling relationship"; the relationship between preload and ESV is a converse relationship.

(b) **Contractility** is the contractile force of the myocardium; this factor has a converse relationship with ESV; that is, the more contractility, the less volume would remain in the ventricle; however, there are a multitude of factors affecting contractility which are discussed later.

(c) **Afterload** is the resistance against the pumping action of ventricles; there is a direct relationship between ESV and afterload; for LV, afterload is mainly the Systemic Vascular Resistance (SVR) which is about 90% of LV afterload; however, Pulmonary Vascular Resistance (PVR) produces about 50% of RV afterload and the RV wall stress is responsible for the other half of RV afterload.

Cardiac Output: abbreviated as CO is the amount of blood that is pumped out of the heart during a 1-min interval; so, CO is the product of SV multiplied by heart rate; so, "cardiac output (mL/min) = stroke volume (mL/beat) × heart rate (beat/min)" or simply: CO = HR × SV.

Ejection Fraction: Another important variable is ejection fraction or more commonly known as "EF." EF is calculated based on this equation: EF = SV/EDV. (In this formula, EDV stands for end-diastolic volume). Usually, EF is expressed in percentage. Normal EF is usually between 55 and 70%; though more than 50% is considered normal for EF and consider patients having EF >50% as good LV performance. EF is directly a very determining index of cardiac function and global clinical outcome. Patients with EF <30% are often considered very high-risk cases impressing the global outcome.

Among the above three main factors (i.e., SV, ESV, and EDV), the cardiac work is much more related to EDV and less to the other 2 factors; this is due to the length-tension concept of sarcomere which affects the cardiac contractility, cardiac work, and cardiac output more than the others. To understand this latter fact, we have to discuss the Frank-Starling relationship in the next paragraph (Germano et al. 1995; Ababneh et al. 2000; Rozanski et al. 2000; Sharir et al. 2006; Lomsky et al. 2008; Mahadevan et al. 2008) (Tables 8, 9, 10 and 11).

Table 8 The main pressures in the cardiovascular system

	Variable
1	Heart rate (HR)
2	Central venous pressure (CVP)
3	Right atrial pressure (RAP)
4	Right ventricular pressure (RVP)
5	Pulmonary artery pressure (PAP)
6	Pulmonary artery wedge pressure (PAWP); Pulmonary capillary wedge pressure (PCWP)
7	Left atrial pressure (LAP)
8	Left ventricular end systolic pressure (LVESP)
9	Left ventricular end diastolic pressure (LVEDP)
10	Aortic pressure

Parts are Modified from Dabbagh A. "Cardiovascular Monitoring"; in "Postoperative Critical Care for Cardiac Surgical Patients." Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp 77-127. Published with kind permission of © Springer, 2014. All Rights Reserved. (2004; Dionne et al. 2012)

Table 9 Calculation formulas of main physiologic variables in the cardiovascular system

	Variable	Formula
1	Cardiac output (CO)	CO = SV × HR
2	Cardiac index (CI)	CI = CO/BSA
3	Stroke volume (SV)	SV = (CO × 1000)/HR
4	Mean arterial pressure (MAP)	MAP = (2DBP + SBP)/3
5	Systemic vascular resistance (SVR)	SVR = [(MAP − CVP) × 80]/CO
6	Pulmonary vascular resistance (PVR)	PVR = [(PAP − PAWP) × 80]/CO

Parts are Modified from Dabbagh A. "Cardiovascular Monitoring"; in "Postoperative Critical Care for Cardiac Surgical Patients." Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp 77-127. Published with kind permission of © Springer, 2014. All Rights Reserved. (Brzezinski 1990; Dionne et al. 2012; Bonafide et al. 2013)

HR heart rate (beats/min), *BSA* body surface area (m^2), *DBP* diastolic blood pressure, *SBP* systolic blood pressure

Table 10 Normal Range of Blood Pressure in *BOYS* with special focus on "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" of the "National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents" 2004 (McLain 1976; Blumenthal et al. 1977; Horan and Sinaiko 1987; Feld and Springate 1988; Brzezinski 1990; Zubrow et al. 1995; Bartosh and Aronson 1999; Dionne et al. 2012; Bonafide et al. 2013; Heys et al. 2013; Shieh et al. 2013; Bassareo and Mercuro 2014; Ingelfinger 2014; Shah et al. 2015)

	DBP (mmHg)		SBP (mmHg)		MAP (mmHg)	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	34–39	54–58	80–89	98–106	49–55	69–75
2	39–44	59–63	84–92	101–110	54–60	73–79
3	44–48	63–67	86–95	104–112	58–64	77–82
4	47–52	66–71	88–97	106–115	61–67	79–86
5	50–55	69–74	90–98	108–116	63–69	82–88
6	53–57	72–76	91–100	109–117	66–71	84–90
7	55–59	74–78	92–101	110–119	67–73	86–92
8	56–61	75–80	94–102	111–120	69–75	87–93
9	57–62	76–81	95–104	113–121	70–76	88–94
10	58–63	77–82	97–106	115–123	71–77	90–96
11	59–63	78–82	99–107	117–125	72–78	91–97
12	59–64	78–83	101–110	119–127	73–79	92–98
13	60–64	79–83	104–112	121–130	75–80	93–99
14	60–65	80–84	106–115	124–132	76–82	95–100
15	61–66	81–85	109–117	126–135	77–83	96–102
16	63–67	82–87	111–120	129–137	79–85	98–104
17	65–70	84–89	114–122	131–140	81–87	100–106

Table 11 Normal Range of Blood Pressure in *GIRLS* with special focus on "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" of the "National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents" 2004 (McLain 1976; Blumenthal et al. 1977; Horan and Sinaiko 1987; Feld and Springate 1988; Brzezinski 1990; Zubrow et al. 1995; Bartosh and Aronson 1999; Dionne et al. 2012; Heys et al. 2013; Bassareo and Mercuro 2014; Ingelfinger 2014; Shah et al. 2015)

	DBP (mmHg)		SBP (mmHg)		MAP (mmHg)	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	38–42	56–60	83–90	100–107	53–58	71–76
2	43–47	61–65	85–91	102–109	57–62	75–80
3	47–51	65–69	86–93	104–110	60–66	78–83
4	50–54	68–72	88–94	105–112	63–67	80–85
5	52–56	70–74	89–96	106–114	64–69	82–87
6	54–58	72–76	91–98	108–115	66–71	84–89
7	55–59	73–77	92–101	110–119	67–73	85–91
8	57–60	75–78	94–102	111–120	69–74	87–92
9	58–61	76–79	95–104	113–121	70–75	88–93
10	59–62	77–80	97–106	115–123	72–77	90–94
11	60–63	78–81	99–107	117–125	73–78	91–96
12	61–64	79–82	102–109	119–126	75–79	92–97
13	62–65	80–83	104–110	121–128	76–80	94–98
14	63–66	81–84	106–112	123–129	77–81	95–99
15	64–67	82–85	107–113	124–131	78–82	96–100
16	64–68	82–86	108–114	125–132	79–83	96–101
17	64–68	82–86	108–115	125–132	81–84	96–101

Frank-Starling Relationship

For the first time, it was in1895 that Otto Frank, the German physician, and physiologist, described the relationship between length and activation of cardiac muscle fibers; the experiment that was completed two decades later by Ernest Henry Starling, an English physiologist and was named "Length Dependent Activation: LDA" or more commonly the "Frank-Starling relationship." Frank and Starling, in their animal model, demonstrated that increased blood accumulation in each ventricle during diastole will result in a proportional increase in the amount of output from the same ventricle during systole (Markwalder and Starling 1914; Patterson et al. 1914; Cingolani et al. 2013; Neves et al. 2015).

This property of cardiac muscle and cardiac fibers is preserved even when they are removed from the body. So, cardiac muscle has a wide range of adaptations against cardiac work; in fact, preload and afterload changes are tolerated and appropriately responded to due to this internal property. Under different physiologic states, the cardiac muscle acts appropriately for different physiologic states: from deep sleep to severe exercise, so the mechanism named Length Dependent Activation (Bollensdorff et al. 2011; Neves et al. 2015).

The basis for the Frank-Starling property of the heart has been explained at different levels: from the cellular level of cardiomyocytes to the neurohormonal control mechanisms of the heart. Based on the Frank-Starling relationship, there is an ***optimal interaction length*** for sarcomere; in the human sarcomere, the "optimal length" is about 2.2 μ for sarcomere which causes the best interaction between actin and myosin (Solaro 2007; Neves et al. 2015).

Each sarcomere has the internal property of length-dependent activation; that is, if the diastolic length of a contractile segment of cardiomyocyte (i.e., sarcomere) increases, then, the generated force of the sarcomere during systole increases proportionally; however, this trend has a plateau. Whenever the plateau is reached, the sarcomere would produce less force during its contractions; hence, Length Dependent Activation. One of the proposed cellular explanations for this finding is that when the sarcomere length is more than the optimal length, the heads of actin and myosin go far from each other; then, their physiologic function impairs and less contraction is produced. On the other side of the spectrum, a sudden decrease in diastolic length of sarcomere results in suppression of force generation; again with a plateau after a while (Solaro 2007; Ribaric and Kordas 2012; Neves et al. 2015).

Though more than 100 years have passed since the findings of Frank and Starling, the exact underlying mechanisms are not fully elucidated yet; especially in the diastolic counterpart of the Frank-Starling Relationship (Campbell 2011; Neves et al. 2015). Today, we know that several different molecular mechanisms cooperate and interact together in each cardiac sarcomere to produce "strain-dependent activation"; but all of the facts are not discovered. At cellular and subcellular levels, some mechanisms have been proposed; some are more important than the others; however, more studies are underway:

1. If diastolic tension increases, the number of cross-bridges will increase; in turn, the overlap status of the cardiac myofilaments improves, which is in favor of more effective contractions; it could be translated that the inter-digitations of actin and myosin in diastole becomes more effective in the production of systolic contractions (de Tombe and Ter Keurs 2015).
2. With the increasing length of the sarcomere, the contractile force is increased in response to each level of Ca^{2+} concentration; so, the increased contractile force is the result of an improved response to Ca^{2+} (Fuchs and Smith 2001; Cingolani et al. 2013; Goldhaber and Philipson 2013).
3. Other proposed mechanisms are not related to "interfilament spacing" or the interaction of actin and myosin; based on these mechanisms, stretch induces some "structural rearrangements" in the thin and thick filaments of the myocardium which result in myofilament length-dependent activation and titin strain (Ait-Mou et al. 2016).

Cardiac Reflexes

Baroreceptors Reflex (or Carotid Sinus Reflex)

This is among the most important reflexes in the cardiovascular system; affecting the hemodynamics of a beat-to-beat pattern. The discovery of different parts of this reflex is the result of the work of many scientists on this reflex and ***chemoreceptor reflex***. These scientists include (but are not limited to): Claude Bernard in 1852; Heinrich Ewald Hering in 1921 and at the same time Jean-François Heymans and his son, Corneille, De Castro in 1925, Edgar Douglas Adrian in 1932, Corneille Heymans in 1938 and Cowley and Arthur C. Guyton during the last decades (Trippodo et al. 1977; Zimmer 2004; De Castro 2009; Estanol et al. 2011). Baroreceptor reflex has some main components:

1. **Importance**: control of blood pressure in the normal range especially for perfusion of vital organs
2. **Stimulus**: severe increase or a severe drop in blood pressure out of the normal values
3. **Response and Physiologic Effect**: compensation for abnormal blood pressure through sympathetic or parasympathetic stimulation leading to modulation of vascular bed tone (decreased vascular tone and hence, drop in blood pressure and bradycardia in case of sudden hypertension; increased vascular tone and hence, rise in blood pressure and tachycardia in case of sudden hypotension). In this way, the baroreceptor reflex leads to regulation of blood pressure and systemic vascular tone, especially if it is highly elevated or there is a severe drop in blood pressure; however, many chronic cardiovascular diseases including chronic hypertension, heart failure, prolonged atherosclerosis, or other systemic diseases like chronic renal disorders, diabetes mellitus or other chronic diseases, impair the reflex partially or totally.
4. **Neural pathway of the reflex:**
   (a) ***Afferent limb*****:** carotid artery body and aortic arch.
   - The receptors of the reflex are circumferential and longitudinal stretch receptors, located in the carotid sinus and aortic arch; these receptors respond to increased blood pressure; then generate impulses.
   - The impulse goes from the carotid sinus through the 9th cranial verve and from the aortic arch through the 10th cranial nerve.
   - Then, the impulses go from these two locations to the ***nucleus solitaries***; which is the central nervous system (CNS) center that processes the input and creates the response.

   (b) ***CNS processing***.
   - ***Nucleus solitaries*** are located in the cardio-regulatory and vasomotor centers of the medulla
   - Two individual segments compose the ***nucleus solitaries***; the first segment is the lateral and rostral segment also called the "pressor center"; the second segment is the central and caudal segment also named the "depressor" center.
   - In these two segments of ***nucleus solitaries***, the afferent signals from the carotid body and aortic arch are integrated with the limbic and hypothalamic inputs; finally, after these neural interactions, the efferent limb of the reflex is created.

   (c) ***Efferent limb***.
   - When the response of the reflex should be towards decreasing blood pressure, decreased sympathetic tone is the main efferent response; which is mainly done through suppression and inhibition of sympathetic pathways; the result is ***hypotension*** and ***bradycardia***; also, systemic vascular tone decreases

which leads to dilatation of blood vessel and systemic vasodilation.
- Increased tone of the ***parasympathetic*** system which is mainly through the vagus nerve and leads to bradycardia and depression of myocardial contractility.
- Finally, blood pressure returns to its normal limits and the triggering of baroreceptors turns off.
- However, in the event of hypotension, the above steps work in the opposite direction to augment systemic vascular tone, augment myocardial contractility, and increase heart rate; that is, the other limb of the reflex would work (Vasquez et al. 1997; Pilowsky and Goodchild 2002; Campagna and Carter 2003; Kashihara 2009).

Bainbridge Reflex

Bainbridge reflex was first described in 1915 by Francis Bainbridge (British physiologist, 1874–1921)

1. What did Francis Bainbridge discover first? He infused "saline or blood into the jugular vein of the anesthetized dog" and observed ***reflex tachycardia***. So, the atrial reflex is another name for this reflex.
2. **Stimulus**: dilation of the main systemic veins, left and right atrium.
3. **Response**: increased heart rate in response to dilation of "the main systemic veins, left and right atrium".
4. **Physiologic effect**: dilation of the right atrium causes activation of its neural pathway; then the signal is processed in CNS, and the response to this afferent impulse is increased sympathetic tone; in turn, increased sympathetic tone leads to increased contractility and tachycardia; finally, increased contractility and tachycardia helps the heart to become empty of the "extra load"; if we want to summarize the Bainbridge reflex, we can simply say: "**Bainbridge reflex causes hypervolemia induced tachycardia**".
5. **Importance**: Bainbridge reflex plays an important role in controlling heart rate and other hemodynamic variables; also, the Bainbridge reflex is contrary to the effects of the "carotid baroreceptor reflex".
6. **Neural pathway** of the reflex:
   (a) **Afferent limb**: the sympathetic neural pathways; the reflex is sensed in the atrial type B mechanoreceptors located in atrial tissue, just located at the junction of venae cavae and right atrial tissue and the junction of pulmonary veins and left atrial tissue; this, in turn, will send an impulse through the vagus nerve (10th cranial nerve) to CNS.
   (b) **Efferent limb**: increased sympathetic drive through CNS to induce tachycardia.
7. How reflex is blocked? if the patient is premedicated with atropine or in animal models, it is blocked by "bilateral vagotomy, or combined cholinergic and beta-adrenergic blockades" (Vatner and Zimpfer 1981; Boettcher et al. 1982; Hakumaki 1987; Hajdu et al. 1991; Barbieri et al. 2002; Crystal and Salem 2012; Cui et al. 2013).

Bezold-Jarisch Reflex

Bezold-Jarisch reflex (BJR) is known as the "cardio-inhibitory" reflex.

1. **Who described the reflex first**: BJR was described first by *von Bezold* and *Hirt* in 1867; *Adolf Jarisch* and *Richter* performed complementary studies in the late 1930s. They described the reflex briefly, especially its triad of "***bradycardia, hypotension, and peripheral vasodilation***" which is usually accompanied by ***hypopnea*** or ***apnea***. Also, coronary artery vasodilation has been mentioned among the items of the reflex. Interestingly, Bezold and Hirt discovered the reflex during their investigations related to the effects of *veratrine* on the heart (Chandler and McDougal 2014).

2. **Importance**: BJR has some cardioprotective effects; in some myocardial stress states like the acute phase of myocardial ischemia, infarction, or reperfusion syndrome, especially in the posterior or inferior myocardial walls, BJR is activated to do its protective effects (Shah and Waxman 2013).
3. **Stimulus**: myocardial stressors like ischemia/reperfusion or infarction.
4. **Response and physiologic effect**: ***parasympathetic*** over-activity is the main underlying phenomenon in BJR; associated with some degrees of ***sympathetic*** inhibition.
5. **Neural pathway** of the reflex:
   (a) **Afferent limb**
      - **Mechanical stimuli** (like volume or pressure overload) or chemical stimuli (like metabolites of myocardial ischemia or some chemicals) trigger some specific receptors inside the heart; located in the left ventricle wall, atrial walls, atrial-caval junctions, and some other chambers of the heart.
      - This trigger starts the pathway of the reflex.
      - The afferent fibers are mainly non-myelinated C fibers and 75% of these afferent fibers are distributed over all chambers of the heart; on the other side, 25% of the afferent fibers are myelinated and are located on the atrial walls and the atrial-caval junctions.

   (b) **CNS processing**
      - The role of the afferent fibers is to inhibit the ***medullary vasomotor center***; located in the medulla oblongata.

   (c) **Efferent limb**
      - When the inhibitory message reaches the medulla, two distinct effects go out of the ***medullary vasomotor center***: bradycardia and suppression of the sympathetic output. Also, there is another indirect effect: decreased sympathetic output suppresses the peripheral vascular tone leading to peripheral vasodilation; systemic hypotension is the final result (Robertson et al. 1985; Hakumaki 1987; Meyrelles et al. 1997; Campagna and Carter 2003; Kashihara et al. 2004; Salo et al. 2007; Kashihara 2009; Iwase et al. 2014).

Chemoreceptor Reflex

Chemoreceptor reflex is the reflex in which changes in partial pressure of arterial oxygen and CO_2 lead to respiratory control; this process is mainly through two pathways: chemoreceptor activation primarily leads to increased drive for ventilatory response and secondarily, to increased sympathetic output which is associated with increased blood pressure.

1. **Importance**: Both peripheral and central chemoreceptors affect and modulate the sympathetic system powerfully; so, they have great impacts on both health and disease; for example, they have a contribution to the generation of some diseases like heart failure, hypertension, and obstructive sleep apnea (Schultz et al. 2015; Lopez-Barneo et al. 2016).
2. **Stimulus**: decreased arterial pressure of oxygen triggers peripheral chemoreceptors in the aortic arch and carotid bodies; while increased arterial pressure of CO_2 (hypercarbia) triggers central chemoreceptors in the brain stem.
3. **Neural pathway** of the reflex.
   (a) **Afferent limb**:
      - There are two main chemoreceptors: peripheral chemoreceptors and central chemoreceptors; peripheral chemoreceptors respond to hypoxia; decreased pressure of oxygen in arterial blood below 80 mm Hg triggers ***peripheral chemoreceptors***, which are located in the carotid body and aortic arch; the set point for hypoxic sensing by the carotid body is mediated in each individual by Hypoxia-Inducible Factor-1 (HIF-1) and HIF-2 (Prabhakar and Semenza 2016). On the other hand, ***central chemoreceptors*** are located in the brain stem and are triggered by hypercarbia (increased CO_2 pressure or decreased pH of the blood).

- afferent nerves are the 9th (glossopharyngeal) and 10th (vagus) cranial nerves.
- These nerves send the impulses to the medulla.

(b) **CNS processing:** rostral ventrolateral medulla is the main central location for processing the inputs from chemoreceptors.

(c) **Efferent limb:** sympathetic pathway is the main efferent limb; however, if hypoxia and hypercarbia persist, the **parasympathetic** pathway is activated**.**

4. **Response and physiologic effect:** the response would be increased sympathetic tone to compensate for hypoxia and hypercarbia; but in the cases of unresolved hypoxia and hypercarbia, the response of the reflex would be altered as **parasympathetic** stimulation which will be presented as bradycardia and coronary vasodilation (both through activation of the vagus nerve) to decrease oxygen demands (Schultz and Sun 2000; Kara et al. 2003; Schultz and Li 2007; Ding et al. 2011; Schultz 2011; Campanucci et al. 2012; Schultz et al. 2012; Schultz and Marcus 2012; Lopez-Barneo et al. 2016).

Valsalva Maneuver

Valsalva maneuver is the name for a cardiac reflex starting with a forced expiration against a "closed glottis."

1. **Who described the reflex first?** The "Valsalva maneuver" was first described by Valsalva in 1704.
2. **Neural pathway.**
   (a) **Afferent limb**: baroreceptors of the arterial system.
   (b) **CNS processing**: medulla.
   (c) **Efferent limb**: sympathetic pathway.
3. **Response and physiologic effect**: due to forced expiration against a closed glottis, intrathoracic pressure increases suddenly with resultant increased central venous pressure (CVP) which subsequently leads to decreased venous return. The result is decreased cardiac output and a drop in blood pressure. However, baroreceptors of the arterial system will sense this blood pressure drop and will start firing the triggering signals for sympathetic stimulation leading to tachycardia.

   Whenever the glottis is opened and venous return resumes, cardiac output and blood pressure are normalized and this will lead to baroreceptor inhibition and "normal heart rate."
4. **Importance**: We usually see a "sequence of rapid changes in preload and afterload stress" during the Valsalva maneuver which is used for some clinical therapeutic and diagnostic implications; for example, for the assessment of the inter-atrial shunts during echocardiography exam (like patent foramen ovale exam); in the assessment of the treatment in supraventricular arrhythmias; or for assessment of the murmurs in hypertrophic cardiomyopathy, atrial septal defect, mitral valve prolapse, pulmonary stenosis, aortic stenosis and tricuspid regurgitation (Sharpey-Schafer 1955; Porth et al. 1984; Nagappan et al. 2002; Zuber et al. 2008; Smith 2012; Wang et al. 2013).

Cushing Reflex

Cushing reflex: This reflex is among the cardiovascular reflexes that aim to protect the brain; other names are "vasopressor response, Cushing reaction, Cushing effect, and Cushing phenomenon" (Dinallo and Waseem 2021). The Cushing reflex is very well known for its triad.

1. **Who described the reflex first?** Harvey Cushing (1869–1939) introduced the Cushing reflex in 1901–1902 (Dinallo and Waseem 2021).
2. **Importance**, **response, and physiologic effect**: the Cushing reflex is an alarm for an abnormal increase in intracranial pressure (ICP); in other words, the Cushing reflex is an important sign of impaired cerebral perfusion status and potential cerebral ischemia. Also, sudden and inadvertent intravenous epineph-

rine administration could elicit the reflex. The reflex is usually seen in the clinic as the following triad:

(a) Bradycardia.
(b) Hypertension (increased systolic blood pressure and wide pulse pressure).
(c) Respiratory depression (respiratory irregularity ending to bradypnea and apnea).

Often an abrupt increase in ICP is due to increased production of cerebrospinal fluid (CSF), decreased CSF reabsorption, or a mass effect in the CNS; in a considerable number of patients, these could be associated with cerebral herniation and death

3. **Stimulus:** increase in ICP; (often) leading to cerebral ischemia.
4. **Neural pathway**
   (a) **Afferent limb:** increased ICP causes impaired CNS perfusion leading to ischemia of the brain which is sensed by perfusion receptors of the brain; these inputs activate the sympathetic pathway.
   (b) **CNS processing:** medulla sends the orders to the sympathetic system.
   (c) **Efferent limb:** sympathetic pathway is activated in an attempt to compensate for reduced cerebral perfusion; alpha 1 adrenergic stimulation is one of the main targets of sympathetic activation which leads to widespread arteriolar vasoconstriction. The resulting clinical picture is increased heart rate, blood pressure, and myocardial contractility**;** however, hypertension is sensed by baroreceptors located in the aortic arch and carotid sinus, and then, reflex bradycardia happens. Finally, increased blood pressure affects the respiratory pattern leading to irregularity in respiration. In this way, the triad of Cushing reflex is completed: hypertension; bradycardia, and respiratory depression (Grady and Blaumanis 1988; Dickinson 1990; Ayling 2002; Fodstad et al. 2006; Molnar et al. 2008; Wan et al. 2008; Robbins et al. 2015; Leyssens et al. 2017; Kenigsberg et al. 2019; Dinallo and Waseem 2021).

Oculocardiac Reflex

Oculocardiac reflex: also known as the Aschner reflex, trigeminal cardiac reflex (TCR), or trigeminovagal reflex (TVR) (Dunville et al. 2021), oculocardiac reflex was first described in 1908 is triggered by traction on the extra-ocular muscles (especially rectus medialis) or it may be elicited by painful stimulation of the eyeball or some other structures of the face. There should be more than a 20% drop in heart rate following the application of force or pressure on the eye globe or extraocular muscles' traction (Dunville et al. 2021). Aging decreases the frequency of occurrence of the reflex. Also, the reflex is somewhat prevented by anticholinergic pretreatment like atropine. The pathway of this reflex is composed of:

1. **Afferent limb**: ophthalmic division of the 5th cranial nerve (trigeminal nerve); the other branches of the trigeminal nerve (maxillary and mandibular branches) might also be involved; the impulses go to CNS via the Gasserian ganglion.
2. **CNS processing:** sensory nucleus of the trigeminal nerve goes through internuncial fibers to the reticular formation and then to the motor nucleus of the vagus nerve.
3. **Efferent limb:** 10th cranial nerve (the Vagus nerve) causing sinus bradycardia as the final clinical presentation of the reflex; at times, junctional rhythms, asystole; other arrhythmias, atrioventricular blocks, or even hypotension may be seen (Arasho et al. 2009; Tsai and Heitz 2012; Bhargava et al. 2014; Meuwly et al. 2015).

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Cardiovascular Pharmacology in Pediatric Patients with Congenital Heart Disease

Ali Dabbagh, Zahra Talebi, and Samira Rajaei

Abstract

The pharmaceutical agents and the chemical molecules affecting the cardiovascular system are among the most important therapies available for health care teams. This chapter aims to give a practical summary of the drugs most commonly used in the perioperative management of congenital heart diseases and their place in the overall treatment plan, while dealing with different agents, including:

- Vasoactive agents
- Inotropes
- Antihypertensive drugs
- Diuretics.
- Adrenoceptor blockers.
- Pulmonary hypertension management pharmaceuticals.
- Anti-arrhythmic agents.
- Analgesics, sedatives, and anesthetic pharmaceuticals.
- The management of pediatric delirium pharmaceuticals.
- Stress ulcer management pharmaceuticals.
- Anticoagulation and thrombolysis pharmaceuticals.
- Blood products and antibiotics used for surgical patients.

The approach used in this chapter is the discussion of each pharmaceutical agent with related dose and the main clinical considerations to present a "concise cookbook of cardiovascular pharmacology"; however, citing specific chapters of the book have been made whenever applicable.

Keywords

Congenital heart disease · Pediatric cardiology · Congenital heart defects Cardiac medications · Congenital heart disease treatment · Pediatric dose

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Vasoactive Agents

Based on general classification, the vasoactive agents could be categorized into two main subclasses:

- Vasoactive agents which affect the arterial system or the venous bed (either vasopressors or vasodilators).
- Inotropes (positive or negative inotropes).

So, the main cardiovascular drugs discussed in this chapter belong to one of the following classes; however, this classification is not comprehensive, and also, there may be some overlaps; in fact, most of these groups currently available pharmaceutical agents share some aspects of each category in variable amounts (Holmes 2005; Bangash et al. 2012; Bracht et al. 2012; Noori and Seri 2012; Jentzer et al. 2015):

1. Pure vasopressors, that is, ***pure vasoconstrictors*** (phenylephrine and vasopressin).
2. Inoconstrictors ***which have both vasoconstrictor and inotropic activity*** (mainly epinephrine, dopamine, and norepinephrine).
3. Inodilators ***which have both vasodilator and inotropic activity*** (mainly milrinone, dobutamine, and levosimendan).
4. Pure vasodilators which affect the arterial system (arterial dilators) and/or the venous system (venodilators); these agents have no inotropic activity (include mainly nitroglycerin, hydralazine, alprostadil, sodium nitroprusside, phentolamine mesylate).

For assessment and prediction of the clinical outcome, some scoring systems have been proposed including the pediatric cardiac inotrope score (PCIS), while similar models are available for adults; these models use the type and dose of any vasoconstrictor/inotrope and predict the clinical outcome; the interested reader is referred to these studies to use any of these online scoring systems for personalized adjustment of in clinical practice (Bangalore et al. 2017; Gupta et al. 2018; Roeleveld and de Klerk 2018; Yamazaki et al. 2018; Bobillo-Perez et al. 2019; Koponen et al. 2019; Song et al. 2021).

When assessing different vasoactive drugs, it is often useful to consider specific receptor responses based on different organs and tissues. The following Tables 1 and 2 are a summary of some of the routinely affected organs (Kee 2003; Trappe et al. 2003; Bangash et al. 2012; Hauser et al. 2017).

Table 1 Receptor types targeted by current vasoactive pharmaceuticals

Specific adrenoceptor	The main target organ(s)	Clinical response
α 1 (including α1A, α1B, α1D)	Arteries, arterioles, veins; however, α effects predominate over β in the splanchnic circulation	Arterial constriction
α 2 (including α2A, α2B, α2C)	Gastrointestinal (GI) tract Cutaneous circulation	Decreased GI tone Decreased motility Decreased amount of GI secretions
β 1	Heart (β 1 >> β 2 in coronary circulation)	Increased heart rate Augmented myocardial contractility
β 2	The vessels of the skeletal muscles	Dilation of the vessels
	Coronary arterial bed	Dilation of the vessels
	Smooth muscles in the tracheobronchial tree	Relaxation of the smooth muscles
β 3	Adipose tissue	Enhancement of lipolysis in adipose tissue, Thermogenesis in skeletal muscle

Modified from Dabbagh A., et al. "Cardiovascular Pharmacology in Pediatric Patients with Congenital Heart Disease"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management". Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp. 117-195.

Table 2 Myocardial receptors characterized by their properties

Receptor type	Chronotropy	Inotropy	Lusitropy	Bathmotropy	Dromotropy
β_1	+	+	+	+	+
M_2	–	–	–	–	–

– decrease, + increase

Modified from Dabbagh A., et al. "Cardiovascular Pharmacology in Pediatric Patients with Congenital Heart Disease"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management". Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp. 117-195.

Pure Vasopressors, That Is, Pure Vasoconstrictors

Phenylephrine

Drug Name: Phenylephrine Hydrochloride

Class: alpha-Adrenergic Agonists

CAS Number: 61-76-7

Mechanism of action: Phenylephrine is a sympathomimetic amine that acts by direct stimulation of peripheral α-1adrenergic receptors. It is used as a bolus or an infusion in the acute management of low systemic blood pressure (BP). The vasoconstriction effect of α-1adrenoceptors may result in reflex bradycardia, although the situation is rarely seen in young children; the patient's heart rate should be carefully monitored when large doses of phenylephrine is administrated (MeenaKumari and Sathyanarayana 2021; Richards et al. 2021).

Phenylephrine has many indications including these:

- ***The most important indication for pediatric patients*** is raising systemic vascular resistance (SVR) in congenital heart disease (CHD) conditions when either ventricle is suffering from an outflow obstruction which is exacerbated with low SVR; such as tetralogy of Fallot (TOF), in which low SVR can cause cyanosis during a "tet Spell," hypertonic cardiomyopathy, etc.
- It is also indicated in patients with partial obstruction in systemic to pulmonary shunt or single ventricle patients with pulmonary stenosis to improve oxygenation.
- Hypotension during anesthesia.
- Septic shock.
- Prolongation of the effects of local anesthetics.
- Prevention and treatment of nasal congestion.
- Hemorrhoids.

Dosing: The common dose of phenylephrine in pediatric patients is as follows: Bolus dosing: 0.5–5 μg/kg or higher, infusion dosing (when frequent bolus doses are needed): 0.02–0.3 μg/kg/min which should be administrated through a central venous catheter if possible.

The Common Adverse Effect of Phenylephrine

- Vasoconstriction of peripheral vascular beds, including skeletal muscle, skin, renal, and mesenteric which can be severe, and compromise the blood flow in vital organs, limiting its use in extreme situations.
- Nausea.
- Vomiting.
- Headache.
- Nervousness.

Cautions: extravasation into the skin and subcutaneous tissues is the main caution when administrating phenylephrine; this can result in ischemia, necrosis, and even tissue loss. Also, the sulfite in phenylephrine formulations can cause hypersensitivity reactions in susceptible individuals.

Vasopressin

Name of Drug: Vasopressin

Class: Pituitary

CAS Number: 11000-17-2

Vasopressin is a vasopressor drug acting through specific vasopressin receptors. Vasopressin

should be used after hemodynamic stability and is usually used in vasodilatory shock, usually when other agents are irresponsive; the effects of vasopressin in refractory shocks have been studied and many believe that low-dose vasopressin is a useful drug for septic shock patients who have already received drugs like norepinephrine infusion (Rizza et al. 2016; Mirhosseini et al. 2017; Bigelow et al. 2019; Datt et al. 2021; Zhou et al. 2021).

Mechanism of action: Vasopressin is the exogenous antidiuretic hormone (ADH) and as a vasopressor that produces intense vasoconstriction (through V1 receptors); also, it has antidiuretic effects (V_2 receptors). When the therapeutic doses of catecholamines are acutely or chronically elevated and hence, adrenergic receptors mare down-regulated, impaired signal transmission in adrenergic receptors occurs, especially when there is concomitant metabolic acidosis; this is why using vasopressin is advantageous in such situations. On the other hand, another potential advantage of vasopressin is that V_2 receptors help create vasodilation to lessen the end-organ hypoperfusion; often, epinephrine or norepinephrine administration may lead to end-organ hypoperfusion in some of the visceral organs (Jahangirifard et al. 2017; Mirhosseini et al. 2017; Amer et al. 2019; Ortoleva et al. 2020; Belletti et al. 2021).

Indications: Vasopressin has many indications in the pediatric population including:

- Diabetes insipidus.
- Polyuria.
- Cardiopulmonary resuscitation (CPR).
- Abdominal radiographic procedures.
- Diagnostic procedures.
- Gastrointestinal hemorrhage.
- Vasodilatory shock.

Its use in treating refractory vasodilatory shock in pediatric patients with cardiogenic and septic etiologies is gaining day to day importance; however, vasopressin is especially useful in cases of low systemic vascular resistance (SVR) brought on by excessive α-adrenergic blockades, such as with phentolamine or phenoxybenzamine (Motta et al. 2005; Mossad et al. 2008; Biban and Gaffuri 2013; Gordon 2016; Mirhosseini et al. 2017; Slovis et al. 2020; Lambert et al. 2021; Zhou et al. 2021).

The usual dose of vasopressin administrated is 0.2–2 mili-units/kg/min infusion, which can be titrated to achieve the desired effect; however, the dose should be weaned and discontinued as soon as possible. Four to eight mili-units/kg/min doses have been reported in some clinical trials to treat vasodilatory shock (Choong and Kissoon 2008; Singh et al. 2009).

Adverse effects associated with low doses of vasopressin are infrequent and mild; however, they increase in frequency and severity with higher doses.

Hypertension and bradycardia may occur due to severe vasospasm and resulting hypertension which induces baroreceptor reflex. Arrhythmia is infrequent. Also, peripheral vasoconstriction may lead to distal limb ischemia. If extravasation occurs, skin necrosis is possible. Hyponatremia is common with vasopressin infusions when prolonged periods of drug infusion are used; therefore, serum sodium should be measured at least daily to prevent this untoward effect. Vasopressin can cause hypersensitivity reactions in susceptible individuals and should be administrated with caution in older children (Sharawy 2014).

Finally, it seems strongly logical to use ***vasopressin as rescue therapy*** and the ***last-resort treatment*** in children with refractory shock (unresponsive to norepinephrine and epinephrine); however, the use of vasopressin should not only be personalized but also, with considerations regarding the underlying clinical state (Meyer et al. 2008; Brissaud et al. 2016; Roeleveld and de Klerk 2018).

Terlipressin is another analog of vasopressin with higher selectivity for V1-receptors; also, it has a longer half-life compared to vasopressin; terlipressin is triglycyl lysine vasopressin and is used in norepinephrine-resistant shocks with a loading dose of 10–20 μg/kg, followed by 1–20 μg/kg/h continuous infusion; however, its pharmacology in pediatric and neonatal patients is under more studies and it may lead to tissue ischemia (Rodríguez-Núñez et al. 2010; Biban and Gaffuri 2013; Erdogan and Bosnak 2017; Saxena et al. 2020; Belletti et al. 2021; Datt et al. 2021).

Inoconstrictors

In the evaluation of catecholamines, one should always keep in mind that the density of adrenoceptors and their response to catecholamines are all markedly affected by several factors; among them, the two have utmost importance:

- The underlying disease.
- The ongoing catecholamine treatment (Bangash et al. 2012; Bracht et al. 2012).

Epinephrine

Name of the drug: epinephrine; adrenalin

CAS number: 51-43-4

Drug group: α & β adrenergic receptor agonist

Mechanism of effect: epinephrine affects all adrenergic receptors including α1, α2, β1, β2 & β2; also, the clinical effects of epinephrine are similar to the effects of sympathetic stimulation with all of its clinical presentations being seen except for its effects on facial arteries and the effects on sweating; epinephrine is assumed as the most potent α adrenergic agonist (Cooper 2008; Jentzer et al. 2015).

Low-dose epinephrine infusions affect mainly the β adrenoceptors. This is why doses of <0.1–0.2 μg/kg/min are usually considered as "pure" inotropic doses, which could improve pump failure after cardiac surgery. However, with increasing the dose, the vasoconstrictor effects of epinephrine are presented much more (Bangash et al. 2012; Noori and Seri 2012; Jentzer et al. 2015).

Epinephrine effects the smooth muscles of bronchi and pupils and leads to bronchial dilation and iris dilation. Glycogenolysis is speeded up in the liver due to epinephrine effects leading to the increased blood level of glucose. Epinephrine could induce myocardial ischemia, tachyarrhythmia, pulmonary hypertension, hyperglycemia, and lactic acidosis. Epinephrine compromises hepatic and splanchnic perfusion, lactate clearance, and oxygen exchange. The decrease in hepatico-splanchnic perfusion in addition to increased hepatic metabolic workload, hypermetabolism, impairment of oxygen exchange, glycolysis, and suppression of insulin release is the main etiologic causes for lactic acidosis and hyperglycemia. Also, epinephrine acts as an antagonist of histamine (Trappe et al. 2003; Bangash et al. 2012; Bracht et al. 2012).

Indications

- **Cardiopulmonary resuscitation and rhythm disturbances**: in such states, these drugs are used to increase coronary perfusion pressure and cerebral perfusion pressure, mainly through α1 adrenergic activity, which increases the diastolic perfusion pressure. However, β adrenergic activity increases the myocardial load and decreased subendocardial perfusion; so, these effects are not optimal; if the patient is in shock due to cardiac problems, epinephrine should be used cautiously due to adverse myocardial effects. Epinephrine is considered the first-line catecholamine agent which is used in cardiopulmonary resuscitation and also, in anaphylactic shock (Rizza et al. 2016; Loomba and Flores 2019; Merchant et al. 2020; Topjian et al. 2020).
- **Bronchospasm**: acts as a rapid bronchodilator in acute bronchospasm and bronchial asthma; however, its unwanted effects on the cardiovascular system mandates using selective β2 agonists in such cases.
- **Anaphylaxis and anaphylactoid reactions**: during life-threatening anaphylaxis reactions and emergencies, the drug is used; the subcutaneous route is usually used in such circumstances; however, in life-threatening emergencies, cautious intravenous (IV) supplements may be considered (Simons and Sampson 2015).
- **Gastrointestinal and renal bleeding:** local intra-arterial administration into the celiac trunk, inferior mesenteric artery, or superior mesenteric artery could be used.
- **As an adjunct to local anesthetics:** could decrease local absorption of the drug.
- **Other uses**: radiation nephritis, control of local skin and/or mucosal bleeding, premature labor, treatment of severe hypoglycemia, as an adjuvant to radio-contrast dyes.

Routes of Administration and Dosage

Epinephrine could be administered through the following routes (Andersen et al. 2015; Hoyme et al. 2017; Merchant et al. 2020; Slovis et al. 2020; Topjian et al. 2020; Yauger et al. 2020):

- Intravenous.
- Intraosseous.
- Intramuscular.
- Subcutaneous.
- Infusion through an intravenous line or central line.
- Through endotracheal tube in cardiopulmonary bypass.
- Inhalational through pulmonary devices like metered-dose inhalers or nebulizers (usually used for children above 4 years).
- Intra-arterial (very rarely; for example, in radiographic assessments).
- Local administration in control for mucosal or skin bleeding.

The clinical dose of Epinephrine classification has been a source of studies; however, it could not be described as a clearcut description; personalized adjustments based on cardiovascular function is necessary; however, a classic classification in pediatric cardiac surgery could be described as follows (Clutter et al. 1980; Kee 2003; Cooper 2008; Kleinman et al. 2010; Watt et al. 2011; Andersen et al. 2015; Atkins et al. 2015; de Caen et al. 2015; Jentzer et al. 2015; Maconochie et al. 2015; Maslov et al. 2015; Lucas et al. 2016; Hoyme et al. 2017; Merchant et al. 2020; Slovis et al. 2020; Topjian et al. 2020; Yauger et al. 2020):

- **Very low-dose** epinephrine is defined as 0.01–0.05 μg/kg/min. This dose of epinephrine does not raise plasma epinephrine levels significantly in such a way to induce major cardiovascular responses; if any response is seen, it will be predominantly due to β-adrenoceptor effects.
- **Low-dose** epinephrine is considered as infusion between 0.05 and 0.1 μg/kg/min; however, low-dose epinephrine causes β2 adrenergic effects (β2 > β1 > α1). The result is a decrease in both systemic vascular resistance (SVR) and blood pressure; however, myocardial contractility increases. As mentioned above, low-dose epinephrine infusions are usually considered as "pure" inotropic doses; this dose improves pump failure after cardiac surgery mainly through β adrenoceptors. Of course, pharmacodynamics studies have demonstrated that heart rate should raise first before any inotropic effect of epinephrine could be exerted.
- **Moderate dose** epinephrine infusion is between 0.1 and 0.5 μg/kg/min; though this dose is not the same in all classifications; in this dose, α1 effects are much more pronounced than the lower doses.
- **High-dose** epinephrine infusion is between 0.5 and 1 μg/kg/min in this higher dose, α1 > β1, β2 leading to increased SVR and increased cardiac index, among the clinical results is a significant increase in diastolic blood pressure. Also, systolic, diastolic, and mean arterial blood pressures are elevated. This dose range may lead to increased plasma levels of glucose and lactate.
- **Very high-dose** epinephrine is when epinephrine infusion dose increases above 1.5 μg/kg/min; as a result, SVR increases significantly; resulting in a significant decrease of the cardiac index. Meanwhile, pulmonary vascular resistance and right ventricular afterload are increased. These events lead to increased myocardial oxygen demand due to increased heart rate and stroke work.
- **During cardiac arrest,** the doses of epinephrine are needed that vasoconstrictive α-effects predominate, to increase diastolic pressure in the root of the aorta leading to improved myocardial perfusion pressure. The desired dose of epinephrine in CPR will be an intravenous bolus of 0.01–0.03 mg/kg every 3–5 minutes. It is not recommended to use doses higher than 1 mg in each 3-5 minutes interval. In refractory bradycardia after cardiac arrest, 0.1–0.2 μg/kg/min as intravenous infusion could be used. Also, intraosseous doses for pediatric cardiac arrest are 0.1 mg/kg up to 1 mg which could be repeated each 3–5 min-

utes. Endotracheal tube administration of epinephrine should be 10 times higher than IV doses (0.1 mg/kg) which could be repeated up to a total dose of 10 mg; the dose could be repeated each 3–5 minutes during the course of CPR; however, the endotracheal dose of epinephrine should be diluted in 5 mL normal saline followed by 5 manual ventilation maneuvers to augment its absorption.

Cautions: epinephrine could lead to dangerous side effects if it is not delivered cautiously; very high blood pressure, myocardial ischemia and chest pain, aortic injures and disruption, or even rupture of cerebral arteries may ensue due to inadvertent injection of the drug, leading to central nervous system (CNS) injuries. In patients with underlying arrhythmia, hypertension, or hyperthyroidism, more caution is necessary. Patients undergoing general anesthesia with volatile agents are at risk of arrhythmias. In patients receiving monoamine oxidase (MAO) inhibitors, simultaneous administration of epinephrine needs extreme caution. Acute angle glaucoma may worsen due to epinephrine. However, in life-threatening conditions, there is no absolute contraindication.

Dopamine

Name of the drug: dopamine hydrochloride

CAS number: 62-31-7

Drug group: selective agonist of β-1 adrenergic receptors

Mechanism of effect: dopamine is a natural catecholamine that is produced in the famous following chain:

L-Phenylalanine is converted to L-Tyrosine, and then it is converted to L-DOPA (L-3,4-**d**ihydr**oxyph**enyl**a**lanine). Then DOPA is changed to dopamine through the enzyme "DOPA decarboxylase".

Dopamine is one of the precursors of norepinephrine. Also, dopamine acts as a neurotransmitter in some of the sympathetic pathways. Besides, dopamine is a major neurotransmitter in some parts of the CNS like the nigrostriatal pathway.

Dopamine has both positive chronotropic and inotropic effects on the myocardium; so, it increases heart rate and myocardial contractility. These effects of dopamine are done through two mechanisms:

- The direct effect which is produced by agonistic effects of dopamine on beta-adrenoceptors.
- The indirect effect which is produced due to the effect of dopamine in releasing norepinephrine from its storage sites in sympathetic nerve endings.

Indications and the Clinical Effects of Dopamine

Often, dopamine is clinically considered as a vasoconstrictor and as an inotrope (i.e., inoconstrictor); however, the effects of dopamine on alpha and beta-adrenergic receptors are weaker than epinephrine or norepinephrine. The clinical effects of dopamine are highly dose-dependent and also, there is inter-individual variability in clinical response. Besides, in different clinical conditions of the same patient, there may be altered responses to dopamine. Keeping these in mind, we may classify the effects of dopamine based on the dose (Kee 2003; Trappe et al. 2003; Cooper 2008; Bangash et al. 2012; Bracht et al. 2012; Md Fauzi et al. 2020; Wen and Xu 2020)**:**

- **Low-dose dopamine** (0.5–2 μg/kg/min): It causes vasodilation which seems to be due to the selective effects of the drug on dopamine receptors which are different from its effects on α and β adrenoceptors (mainly on mesenteric, renal, intracerebral and coronary vascular beds); haloperidol acts as an antagonist to these receptors. Increased glomerular filtration rate, increased renal blood flow, increased renal excretion of sodium, and increased urine flow are among the main results of this dopamine dose; often, increased renal blood flow does not affect urine osmolality. However, the so-called "renal-dose dopamine" which is the same as low-dose dopamine is not supported by evidence for renal protection. Total peripheral vascular resistance is usually not altered so much in this dose (0.5–2 μg/kg/minute) because it would be raised by alpha activity.

- **Medium-dose dopamine** (2–10 μg/kg/min): It mainly stimulates β-1 adrenoceptors and increases myocardial contractility. Also, this drug dose augments stimulation of the sino-atrial node and increases impulse conduction in myocardial tissue. β2 adrenoceptors, which cause peripheral vasodilation, are usually not stimulated by this dose (i.e., 2–10 μg/kg/minute). However, the degree of increased myocardial oxygen consumption by dopamine is less than isoproterenol. Also, dopamine increases systolic blood pressure and pulse pressure, while diastolic blood pressure is not much affected. As mentioned, in low-to-moderate doses of dopamine, total peripheral vascular resistance is usually not altered so much (because it would be raised by alpha activity). So, as a result of relatively constant vascular resistance and increased cardiac output, perfusion in the vascular bed is increased with 2–10 μg/kg/min dose. Often, tachyarrhythmia is not a frequent result of dopamine use.
- **High-dose dopamine** (10–20 μg/kg/min): The effects of dopamine in these doses are mainly α adrenoceptor stimulation especially when the dose goes above 15 μg/kg/min; the clinical result is vasoconstriction and increased blood pressure. The vasoconstrictive effect is first seen in muscular arterial tone; however, renal and mesenteric vessels are affected and with increased doses of the drug. Very high dopamine doses (i.e., doses above 20 μg/kg/min) may lead to ischemia in the aforementioned organs, including limbs; so, doses above 20 μg/kg/min may compromise the circulation of the limbs and we may consider the effects of this very high dose as similar to the effects of norepinephrine.

Dopaminergic Activity: Its Effect on the Immunologic and Neurohormonal Systems

There is increasing evidence that there are very important interactions between the dopaminergic system and many aspects of the neurohormonal system including a decline in the secretion of prolactin, thyroid, and growth hormones and increased synthesis of the glucocorticoid hormones; these effects are especially important in the critically ill and septic patients (Van den Berghe and de Zegher 1996; Md Fauzi et al. 2020; Wen and Xu 2020).

Besides, there are great interactions between dopamine and the immunologic system; both in health and disease. Dopamine could play a crucial role in the modulation of the immunologic and inflammatory response. These immunomodulatory effects of dopamine are dose-dependent and mediated through different dopamine receptors (Table 3):

- The first family of dopaminergic like receptors which is known as D1 receptors and includes D1 and D5; and the second family of dopaminergic like receptors which is known as D2 receptors and includes D2, D3, and D4;

Table 3 A summary of the effects of dopamine doses and their effects

	Type of affected receptor(s)					
Dose of dopamine	α 1 adrenoceptor	α 2 adrenoceptor	β 1 adrenoceptor	β 2 adrenoceptor	Dopamine 1 receptor (D1)	Dopamine 2 receptor (D2)
0.5–2 μg/kg/min	0	0	+	0	+++	+++
2–10 μg/kg/min	+	+	+++	+++	++++	++++
10–20 μg/kg/min	+++	+	+++	+	++++	++++

+ increase, − decrease, 0 no change

Modified from Dabbagh A., et al. "Cardiovascular Pharmacology in Pediatric Patients with Congenital Heart Disease"; in "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management". Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp. 117-195. Published with kind permission of © SpringerNature, 2017. All Rights Reserved

besides, these immunomodulatory effects are mediated through α and β adrenergic receptors (Elenkov et al. 2000; Beck et al. 2004; Franz et al. 2015; Levite 2016; Feng and Lu 2021).
- Dopamine affects the cytokine network, leading to decreased expression of adhesion molecules, suppression of the production trend in cytokine and chemokine network, decreased potency of neutrophil in producing chemotaxis, and impaired proliferation of T-cell population (Elenkov et al. 2000; Beck et al. 2004; Franz et al. 2015; Levite 2016; Álvarez-Luquín et al. 2021; Levite 2021; Penedo et al. 2021).
- Dopamine receptors are expressed in T lymphocytes leading to modulation of this cell population; this effect is mediated through both the dopaminergic D1 receptors (D1/D5) and the dopaminergic D2 receptors (D2/D3/D4) (Elenkov et al. 2000; Zhao et al. 2013; Franz et al. 2015).
- The cytotoxic effects of natural killer cells are highly affected by dopamine receptors: D1 receptors (D1/D5) facilitate the activity of natural killer cells; however, D2 receptors (D2/D3/D4) suppress the activity of natural killer cells (Zhao et al. 2013; Franz et al. 2015; Capellino et al. 2020).
- Dendritic cells (DC's) are the main part of the innate immunity system; also they act as a very important linker between innate and adaptive immune systems with a very crucial role in the activation of the adaptive immune system. DC's affect the whole dopaminergic system in nearly all aspects which yields to increased production and storage of dopamine; in turn, DC's stimulate the D1 and D2 receptors in an autocrine manner (Prado et al. 2013; Pacheco et al. 2014; Franz et al. 2015; Herrera et al. 2015; Levite 2016).
- Dopamine could augment differentiation of CD4(+) T cells to T helper 1, T helper 2, and T helper 17 cell lines; these are inflammatory T cells (Prado et al. 2013; Franz et al. 2015; Herrera et al. 2015; Levite 2016).
- On the other hand, regulatory T cells may lead to the release of large amounts of dopamine that can also release high amounts of dopamine; then, dopamine, in an autocrine/paracrine manner, through dopamine receptors, suppresses the effects of regulatory T cells; this effect of dopamine through regulatory T cells is in favor of inflammatory process and autoimmunity (Pacheco et al. 2014; Franz et al. 2015; Herrera et al. 2015; CID=681 2016; Levite 2016, 2021).

Time of effect: during the first 5 min after commencing dopamine infusion, its effects are started; meanwhile, the plasma half-life of dopamine is about 2 min; so, it takes less than 10 min for systemic effects of dopamine to be disappeared. In patients using monoamine oxidase (MAO) inhibitors, the drug effect may be as long as 1 h; which mandates careful attention.

Indications

1. Shock: to increase cardiac output, blood pressure, and urinary flow; of course, volume replacement should be done first. Also, dopamine is used to increase systemic vascular resistance in these patients.
2. Acute renal failure: though doses less than 5 μg/kg/min affect the dopaminergic receptors and may increase renal and mesenteric perfusion, no improvements in glomerular filtration rate (GFR) is seen; no significant evidence is available that dopamine could improve the oliguric state in the critically ill patients.
3. Hepatorenal syndrome: as part of the therapeutic protocol in such patients; however, long-term treatment is not associated with significant effects.
4. Cirrhosis: as part of the therapeutic regime is used; no proof for its long-term effects.
5. Cardiopulmonary resuscitation: as part of advanced cardiac life support (ACLS) to increase cardiac output and blood pressure.
6. Heart failure: in refractory cases with no significant improvement with cardiac glycosides and diuretics, dopamine could be used in short term to increase cardiac output and blood pressure.

Dopamine dosage and administration: Dopamine is usually administrated by intrave-

nous infusion (bolus administration should be avoided); however, in certain situations, where intravenous infusion is not possible, it might be administrated through intra-osseous infusion.

The intravenous infusion of dopamine should be done through central or at least, large peripheral veins, preferably the antecubital vein; also, it is better to use an infusion pump to control the rate of flow; the dorsal veins of the hand and ankle can increase the risk of extravasations and therefore should be avoided; usually, DW5% is used to dilute dopamine and achieve subsequent concentrations of 400, 800, 1600, and 3200 μg/mL of dopamine. The 3200 μg/mL concentration is used when higher concentrations are needed in patients with fluid restriction (Kee 2003; Jentzer et al. 2015; CID=681 2016; Rizza et al. 2016; Olivares-Hernández et al. 2021; Sonne et al. 2021).

Specific considerations for children: dopamine can be used at any age, the rate of administration is different in every individual, and it should be titrated to reach the desired response. The usual rate of administration in pediatric shock and CPR, and as an inotropic agent to assist weaning from cardiopulmonary bypass in children, and in the early postoperative period is starting with 2–5 μg/kg/min and then increasing the dose 1–4 μg/kg/min every 10–30 min to achieve the optimal response. Most patients are controlled with 5–15 μg/kg/min. Infusion rates higher than 20 μg/kg/min can cause excessive vasoconstriction.

Clearance of dopamine is not predictable in young children, especially neonates and it can be up to two times higher in children younger than 2 years old; also neonates are more sensitive to vasoconstrictor properties of dopamine. Occasionally, doses as high as 50 μg/kg/min are needed for younger children. Some clinicians have avoided dopamine due to its potential to cross the blood–brain barrier and suppress pituitary hormones like thyroid releasing hormone, in pediatric patients. These potential adverse effects are not seen with other natural or synthetic catecholamines.

Common adverse effects: Tachycardia, angina, palpitation, vasoconstriction, hypotension, dyspnea, nausea, vomiting, and headaches.

Warnings and Contraindications:

- In patients who have been previously (within 2–3 weeks of dopamine administrations) treated with MAOIs, dopamine dose should be reduced.
- The patient's plasma volume and electrolytes should be monitored to avoid overhydration while administrating IV fluids.
- Sensitive reactions are probable in patients allergic to sulfite (present in some formulations) or corn products (present in dextrose IV solutions).
- Dopamine is contraindicated in patients with pheochromocytoma or uncorrected tachyarrhythmias or ventricular fibrillation (VF).

General Precautions

The patients' general condition, electrocardiogram (ECG), BP, and urine flow and, also preferably cardiac output and pulmonary wedge pressure should be monitored carefully before and during the treatment with dopamine to avoid the incidence or exacerbation of any of the following conditions: extravasation, hypovolemia, hypoxia, hypercapnia, and acidosis, vasoconstriction, hypotension, occlusive vascular disease, ventricular arrhythmias, ischemic heart disease, and diabetes mellitus (caution in administrating dextrose).

To discontinue dopamine infusion, the dose of dopamine should be decreased gradually while expanding blood volume with IV fluids to prevent a recurrence of hypotension.

Norepinephrine

Name of Drug: Norepinephrine Bitartrate (Levophed)

Class: Alpha- and beta-Adrenergic Agonists

CAS Number: 69815-49-2

Norepinephrine, a very potent vasoconstrictor, is among the naturally occurring catecholamines and is mainly released by the postganglionic adrenergic nerve endings and the adrenal medulla (10–20%). Part of the effect of norepinephrine is similar to epinephrine, that is, it works by stimulating the β-1 adrenoceptors on the heart and therefore increasing the myocardial contractility

(Rizza et al. 2016; Smith and Maani 2021). During the last years, the trend of norepinephrine use as a vasopressor for postoperative pediatric cardiac patients has been somewhat replaced by vasopressin (Loomba and Flores 2019).

The variation in the clinical use of epinephrine and norepinephrine is due to their difference in peripheral function. Norepinephrine is a potent α-1 agonist with little to no effects on β-2 receptors responsible for vasodilatation; therefore, it increases the SVR and blood pressure even with low doses. Cardiac output is usually decreased or unchanged, and heart rate may be reduced as a result of the reflex increase in vagal tone. Both drugs can cause hyperglycemia in prolonged infusions, with norepinephrine causing these effects at much higher doses than epinephrine.

Indications

The main indication of epinephrine is in the treatment of disease states when other vasopressor agents fail and there is a need for a very potent vasoconstrictor; the main examples are refractory shock due to any cause or vasoplegia syndrome (including vasoplegia syndrome after cardiopulmonary bypass); the following are a list of indications for norepinephrine use (De Backer et al. 2010; Mossad et al. 2011; Bangash et al. 2012; Vasu et al. 2012; Mehta et al. 2013; Rizza et al. 2016; Rossano et al. 2016; Mirhosseini et al. 2017; Sponholz et al. 2020; Datt et al. 2021; Lambert et al. 2021):

- Shock: for vasoconstriction and cardiac stimulation in the treatment of shock that persists after adequate fluid volume replacement and in cases of profound vasodilatory shock unresponsive to high doses of dopamine or dobutamine, such as sepsis in neonates.
- Anaphylactic shock: vasopressor agents, such as norepinephrine can be used for maintaining blood pressure in patients with anaphylactic shock, but epinephrine is the drug of choice in these situations.
- Myocardial infarction: to treat the hypotension in selected cases.
- CPR: may be used for ACLS when severe hypotension (e.g., SBP <70 mmHg) and low total peripheral resistance persist with less potent drugs.
- Hypotension during anesthesia: it is among a list of alternatives; however, agents like intravenous ephedrine or phenylephrine or other vasopressors are used much more commonly.
- Adjunct to local anesthetics: to decrease the rate of vascular absorption of the anesthetic, and hence, increasing the duration of anesthesia; however, epinephrine is used much more commonly for this purpose.
- GI Hemorrhage: intraperitoneally or via a nasogastric tube as a hemostatic agent for severe upper GI bleeding.
- Pericardial tamponade to temporarily increase cardiac filling pressure and cardiac output.

Dose and Administration

The epinephrine use is often by intravenous (IV) infusion using an infusion pump or other apparatus to control the rate of flow, and into the antecubital vein of the arm or femoral vein. Norepinephrine should not be administered in the same IV line as alkaline solutions, which may inactivate the drug. Extravasation may result in local necrosis and must be carefully avoided. It is suggested to change the injection site periodically in prolonged therapy.

The dose range of norepinephrine infusion in pediatric cardiac patients varies from 0.02 to 0.2 μg/kg/min. And it is better to be administered in the lowest effective dosage for the shortest possible time.

In shock usually, a dose of 2 or 2 μg/m^2 per min is administrated. In Pediatric Advanced Life Support (PALS) during CPR, 0.1–2 μg/kg/min is infused intravenously as an adjunct to therapy until reaching the optimum blood pressure and perfusion (De Backer et al. 2010; Mossad et al. 2011; Vasu et al. 2012; Rossano et al. 2016; Loomba and Flores 2019).

Warnings and Contraindications:

- Norepinephrine is contraindicated during anesthesia with cyclopropane or halogenated hydrocarbon general anesthetics; though they are rarely used in the current era. Also use in fingers, toes, ears, nose, or genitalia in con-

junction with local anesthetics is contraindicated.
- The following conditions should be thoroughly monitored in patients treated with norepinephrine: hypovolemia, as vasopressor therapy is not a substitute for replacement of blood, plasma, fluids, and/or electrolytes, hypoxia, hypercapnia, and acidosis, extravasation (injection into leg veins should be avoided, especially in geriatric patients or those with occlusive vascular diseases, arteriosclerosis, diabetes mellitus, or Buerger's disease), hypertensive or hyperthyroid patients (increased risk of adverse reactions due to hypersensitivity to this drug), peripheral or mesenteric vascular thrombosis, sensitivity reactions (in sulfite-sensitive patients because the formulation contains sulfites).

General Precautions

The following are the main precautions in using norepinephrine (De Backer et al. 2010; Mossad et al. 2011; Bangash et al. 2012; Vasu et al. 2012; Mehta et al. 2013; Rizza et al. 2016; Rossano et al. 2016; Kumar 2020; Sponholz et al. 2020) (Table 4):

- Prolonged administration: as it may cause decreased cardiac output, edema, hemorrhage, focal myocarditis, subpericardial hemorrhage, necrosis of the intestine, or hepatic and renal necrosis which is seen mostly in patients with severe shock and can be due to the shock itself.
- Cardiovascular and renal effects: Severe vasoconstriction and limiting the blood flow in vital organs.
- Increases myocardial oxygen consumption and the work of the heart.
- Venous return to the heart may be reduced due to increased peripheral vascular resistance, which can ultimately reduce cardiac output.
- Arrhythmias: especially likely to occur in patients with acute MI, hypoxia, or hypercapnia, or those receiving other drugs increasing cardiac irritability such as cyclopropane or halogenated hydrocarbon general anesthetics.
- Common adverse effects: dizziness, tremor, respiratory difficulty, headaches.

Inodilators (Mainly Milrinone, Dobutamine, and Levosimendan)

The inodilators are primarily milrinone, dobutamine, and levosimendan. A summary of their characteristics could be found in Table 5.

Milrinone

Name of the drug: milrinone lactate

CAS number: 78415-72-2

Drug group: cardiotonic drug; phosphodiesterase III inhibitor

Mechanism of effect: milrinone is a positive inotropic agent and an arterial dilator with weak chronotropic effects; besides, it has cardiac lusitropy effects; regarding overall cardiac function, milrinone improves the cardiac output, while augmenting the coupling between the left ventricle and the arterial tree; however, the final result would be enhanced efficiency of the cardiac pump (Ayres and Maani 2021; Vogel et al. 2021). The drug mechanisms are different from catecholamine agents. Due to its effects, milrinone is commonly known as an "***inodilator***"; its mechanism of action is through inhibition of phosphodiesterase (PDE) III isoenzyme in cardiomyocytes and vascular smooth muscle cells; the action of PDE III is to degrade cyclic adenosine monophosphate (cAMP) and when it is inhibited, intracellular cAMP levels are peaked up which in turn leads to increased activation of protein kinase A (PKA). With the increased action of PKA, many cellular structures of cardiomyocytes like calcium channels and contractile elements are activated. One of the most important roles of cAMP is to activate protein kinase A (PKA)-mediated phosphorylation of multiple target proteins (Knight and Yan 2012; Ferrer-Barba et al. 2016; Thorlacius et al. 2021).

PDE III is one subfamily of the great family of PDEs; there are 11 subfamilies of PDEs over different tissues; among them, 6 subfamilies function inside cardiac myocytes. One of the main roles of the PDE family is to modulate the intracellular cyclic adenosine monophosphate (cAMP) and/or cyclic guanosine monophosphate (cGMP), to regulate the dynamic interactions between PDEs, cardiac β-adrenergic, PKA, and the process of "synthesis and hydrolysis" of

Table 4 A summary of the main vasopressor agents

Drug	Dose	Receptors	Inotropy	HR	SVR	PVR	Renal vascular resistance	Half-life	Adverse effects
Epinephrine	Cardiac arrest:	Lower doses:	+	+	0,–	0,–	–	<2 min	Tachyarrhythmias
	Children:	$\beta_1,\beta_2 > \alpha_1$							If extravasation occurs, skin necrosis is possible
	IV bolus: 0.01 mg/kg every 3–5 min	Higher doses:							
	Low cardiac output:	$\alpha_1 > \beta_1,\beta_2$	+	+	+	+	+		
	Continuous IV infusion: 0.01–1 μg/kg/min								
Norepinephrine	Continuous IV infusion: 0.05–0.3 μg/kg/min (maximum dose: 2 μg/kg/min)	$\alpha_1 > \beta_1,\beta_2$	+	+	+	+	–	<2 min	Hypertension Bradycardia Myocardial ischemia If extravasation occurs, skin necrosis is possible
Dopamine	Continuous IV infusion:							2 min	Hypertension, tachyarrhythmias
	2–5 μg/kg/min	DA_1, DA_2	0	0	0	0	–		
	5–10 μg/kg/min	$\beta_1,\beta_2 > \alpha_1$	+	+	0,–	0	0		
	10–20 μg/kg/min	$\alpha_1 > \beta_1,\beta_2$	+	+	+	+	+		
Dobutamine	Continuous IV infusion: 2–20 μg/kg/min	$\beta_1 > \alpha_1,\beta_2$	+	+	–	–	0	2 min	Tachyarrhythmias
Isoproterenol	Continuous IV infusion: 0.01–0.2 μg/kg/min	β_1,β_2	+	+	–	–	–	8–50 min	Tachyarrhythmias
Calcium Chloride	5–10 mg/kg IV bolus; 10 mg/kg/h infusion 20 mg/kg intra cardiac (in ventricular cavity)	Contractile proteins	+	0,–	+	0,+	0	N/A	Hypertension
Milrinone	Continuous IV infusion: 0.25–0.75 μg/kg/min	Phosphodiesterase III, inhibitor/↑ cAMP	+	+	–	–	–	Infants: 3.15 0 2 h Children: 1.86 0 2 h	Hypotension, ventricular arrhythmias, headache

(continued)

Table 4 (continued)

Drug	Dose	Receptors	Inotropy	HR	SVR	PVR	Renal vascular resistance	Half-life	Adverse effects
Nesiritide	Continuous I.V. Infusion: 0.01 μg/kg/min; if necessary, titrate by 0.005 μg/kg/min every 3 h to maximum of 0.03 μg/kg/min[a]	B-Natriuretic peptide	0	0	–	–	+	60 min	Hypotension, increased levels of serum creatinine
Levosimendan	6–12 μg/kg load; 0.05–0.1 μg/kg/min	Troponin C, increasing Ca^{2+}sensitivity; ATP-sensitive K^+ channels for vasodilation	+	0	–	–	–	1 h	Hypotension, tachyarrhythmias, nausea, headache
Digoxin	Oral: 5–15 μg/kg/day divided every 12 h IV: 4–12 μg/kg/d divided every 12 h	inhibition of the Na+/K+ ATPase in the myocardium	+	–	–	–	–	Infants: 18–25 h Children: 35 h	Nausea and vomiting Dizziness, headache, dysrhythmia
Phenylephrine	Bolus intravenous dose: 5–20 μg/kg which could be repeated each 10–20 min Intravenous infusion dose: 0.1–0.5 μg/kg/min Increase/decrease rate of infusion by a minimum of 10 μg/min at intervals no longer than Q 15 min Titration parameter: MAP; SBP adjusted for age	Selective α1 agonist	0/+	0/– May decrease heart rate if blood pressure goes very high	+++	0/+	++	5 min	Bradycardia, arrhythmia, myocardial ischemia If extravasation occurs, skin necrosis is possible
Vasopressin	0.04 units/min	Agonist of vasopressin 1 (V1) receptors	0	0	+	0		10–30 min	Hypertension Bradycardia Arrhythmia Vasoconstriction Distal limb ischemia If extravasation occurs, skin necrosis is possible

Modified from Fellin R. "Cardiovascular Pharmacology"; in "Postoperative Critical Care for Cardiac Surgical Patients". Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp. 41-72. Published with kind permission of © Springer, 2014. All Rights Reserved

+ increase, – decrease, 0 no change

v vasopressin, *HR* heart rate, *SVR* systemic vascular resistance, *PVR* pulmonary vascular resistance, *DA* dopamine, *cAMP* cyclic adenosine monophosphate, *cGMP* cyclic guanosine mono phosphate

[a]Recommended dose in Moss and Adams Heart disease in infants, children and adolescent 2013: 1 μg/kg load; 0.1–0.2 μg/kg/min

Table 5 A summary and comparison between the main inodilators regarding their pharmacological properties in pediatrics

Drug	Dose	HR	MAP	PCWP	CO	SVR	Adverse effects
Milrinone	0.25–0.75 μg/kg/min Increase/decrease by a minimum of 0.125 μg/kg/min at intervals no longer than Q 6 h ***Parameters for titration of the drug***: blood pressure; CO; CI	0/+	0/–	–	+	–	Arrhythmia, thrombocytopenia, myocardial ischemia, hypotension/vasodilation ***No increase*** in myocardial oxygen demand
Dobutamine	2.5–20 μg/kg/min Increase/decrease by 1 μg/kg/min at intervals no longer than Q 30 min ***Parameters for titration of the drug***: blood pressure; CO; CI	0/+	0	–	+	–	Arrhythmia may potentiate hypokalemia, increases myocardial oxygen demand and so, may lead to myocardial ischemia, hypotension/vasodilation
Levosimendan	Loading dose: 6–12 μg/kg over 10 min then intravenous infusion of 0.05–0.2 μg/kg/min	0/+	0/–	–	+		Headache and/or hypotension may be induced due to vasodilatory effects of drug ***No*** risk of arrhythmia ***No*** renal or hepatic dose adjustment needed ***No increase*** in myocardial oxygen demand

+ increase, – decrease, 0 no change

cAMP and cGMP; these are elements of myocardial cells and the contractile processes; more details could be found in chapter "Cardiovascular Physiology" (Conti and Beavo 2007; Yan et al. 2007; Zaccolo and Movsesian 2007; Miller and Yan 2010; Azevedo et al. 2014; Ahmad et al. 2015; Zhao et al. 2015, 2016; Brescia and Zaccolo 2016; Thorlacius et al. 2021).

In smooth muscle cells of the arterial system, PKA leads to relaxation of the vessel walls. However, milrinone does not affect beta-adrenergic activity nor it blocks the activity of Na/K ATPase activity like cardiac glycosides. The positive inotropic effects of milrinone are presented as augmented myocardial contractility and improved Frank-Starling curve in patients with perioperative low cardiac output state. In addition to augmentation of systolic function, milrinone improves diastolic relaxation of the myocardial tissue, leading to improved diastolic function. The inodilator effects of milrinone are seen when the plasma level of the drug is in the range of 100–300 ng/mL (Begum et al. 2011; Knight and Yan 2012; Majure et al. 2013; Brunner et al. 2014; Bianchi et al. 2015; Ferrer-Barba et al. 2016; Gist et al. 2016).

Indications

Milrinone is primarily used for the following uses (DiNardo and Nasr 2021; Kanazawa et al. 2021; Thorlacius et al. 2021):

- Perioperative low cardiac output state (LCOS); including systolic and/or diastolic dysfunction of the myocardial tissue.
- In heart failure patients (including cardiogenic shock) milrinone is used for acute term treatment; however, its effectiveness in long-term treatment of heart failure is not confirmed yet.
- Pulmonary hypertension; especially in cases of *perioperative pulmonary hypertensive crisis* (some studies have demonstrated inhalational use as the method of choice for such patients).

Drug Dose

- **Loading dose**: 25–75 μg/kg (in patients undergoing cardiopulmonary bypass, this loading dose is often administered as a bolus dose during CPB); however, if the patient is not under cardiopulmonary bypass, this loading dose should be administered intravenously in 10-60 minutes, with vigilant control of blood pressure.
- **Maintenance dose**: 0.25–0.75 μg/kg/min as an intravenous infusion; the loading dose can be avoided to prevent the initial hypotension and the treatment can begin with the infusion, recognizing that therapeutic plasma levels will not be achieved for several hours.

These doses lead to the desired plasma level of 100–300 ng/mL; meanwhile, in patients with acute kidney injury, especially in the neonates, infants, and children, there should be personalized dose modification; however, milrinone is metabolized mainly through kidneys (Gist et al. 2016; Hornik et al. 2019; Mizuno et al. 2019; Ayres and Maani 2021).

Routes of Administration

Milrinone is infused primarily through the intravenous route, either peripheral or central lines; however, during cardiopulmonary bypass, a bolus dose of the drug could be administered through the ports of the bypass circuit. Some studies have demonstrated these alternative routes; their efficacy is to be determined (Brunner et al. 2014; Ogawa et al. 2014; Ventetuolo and Klinger 2014; Liu et al. 2021; Vogel et al. 2021):

- Intraosseous (e.g., during cardiopulmonary resuscitation when there is no intravenous line).
- The inhalational route is especially in pulmonary hypertension crisis and cardiac transplant patients; in these patients, milrinone is selectively absorbed by the pulmonary vascular system; the result would prevent hypotension and possibly improve oxygenation in the lungs.
- The oral route; not a routine method since it is claimed to increase morbidity.

The primary bolus dose and then, the maintenance dose of milrinone could be diluted with these solutions:

- Half saline.
- Normal saline.
- Normal saline with 5% dextrose.

Adverse Effects and Pharmaceutical Precautions

- One of the main contraindications of milrinone is hypersensitivity to the drug or any of its formulations.
- Obstructive valve lesions, especially diseases like hypertrophic subaortic stenosis, aortic valve stenosis, or pulmonary valve stenosis; in such patients, pending on the severity of stenosis, milrinone may be prohibited, or at least, its use must be with strict caution.
- Decreased impulse delay in atrioventricular (AV) node which might lead to an increased ventricular response in patients with underlying atrial flutter or atrial fibrillation; it is recommended to start cardiac glycosides before milrinone in these patients (Fleming et al. 2008); also, it has been demonstrated that in congenital heart surgery, milrinone is "an independent risk factor for clinically significant early postoperative tachyarrhythmias" (Smith et al. 2011).
- Currently, there is not enough data to support intravenous or oral administration of milrinone for periods more than 48 hours; overwhelming intracellular accumulation of cAMP has been proposed as the underlying mechanism for such untoward effects; it might lead to arrhythmias.
- In patients on diuretics, adding milrinone may lead to increased renal perfusion and potential electrolyte abnormalities.
- Decreased ventricular filling pressures may result in severe hypotension which mandates hemodynamic vigilance while starting the drug.

Dobutamine

Mechanism of action: Dobutamine which is a synthetic congener of dopamine mainly acts as a pure positive inotropic agent through adrenergic recep-

tors. It does not affect DA receptors or the release of norepinephrine from nerve endings. Dobutamine mainly targets β1 receptors and its effects on β2 or α1 receptors are less pronounced. Dobutamine produces a reduction in systemic vascular resistance with only a modest increase in heart rate and blood pressure, which is its most important advantage over dopamine and can be beneficial in patients with ventricular dysfunction.

Indications: Indicated in cardiac decompensation and shock, acute heart failure, low cardiac output state after open-heart surgery, neonates with asphyxia, myocarditis, MI, and after open-heart surgery.

Dosage: Given as continuous IV infusion in a dose of 2–20 μg/kg/min. Doses more than 20 μg/kg/min may produce tachycardia and ventricular ectopy and could induce or exacerbate myocardial ischemia. The concentration used is individualized depending on each patient's drug and fluid requirements but should not exceed 5000 μg/mL (= 5 mg/mL). Infusion of dobutamine should be gradually tapered after 48–72 h of administration. In patients with hypotension, dopamine or noradrenaline infusion may be used concomitantly with dobutamine.

Side effects: Ectopic heartbeats, increased heart rate, elevations in BP, hypotension, phlebitis, local inflammatory changes.

Contraindications: Contraindicated in obstructive lesions of heart, cardiac arrhythmias. Hypovolemia must be corrected before dobutamine administration. Compared with milrinone, dobutamine shows a more profound decrease in left ventricular filling pressures and vascular resistance than phosphodiesterase inhibitors and is more likely to increase heart rate. When compared to isoproterenol, dobutamine causes less improvement in the automaticity of the sinoatrial (SA) node (Kee 2003; Holmes 2005; Noori and Seri 2012; Jentzer et al. 2015; Rossano et al. 2016; Cavigelli-Brunner et al. 2018; Wang et al. 2020).

Levosimendan

Levosimendan is a myocyte calcium sensitizer that is used mainly for the treatment of acute decompensated heart failure and/or low cardiac output states in some countries. However, in some other countries including the US, levosimendan is not licensed. Also, several trials have been done in pediatric patients demonstrating its efficacy in pediatric congenital heart disease. Its mechanism of action is through increasing myocyte calcium sensitivity by attaching to cardiac troponin C (TnC); this effect is mediated through a calcium-dependent mechanism, but its vasodilatory effects are mediated through opening ATP-sensitive potassium channels; due to these mechanisms, levosimendan does not increase myocardial oxygen demand; instead, it has cardioprotective effects through activation of ATP-sensitive K channels in the mitochondria.

Levosimendan needs no renal or hepatic dose adjustment. Its main complications include headache and/or hypotension due to vasodilatory effects of the drug; however, there is no risk of arrhythmia.

The loading dose of levosimendan is 6–12 μg/kg administered intravenously over 10 minutes followed by continuous intravenous infusion of 0.05–0.2 μg/kg/min; time to start of effect is 5 min; whit peak effects being observed in 10 to 30 min; the time duration of levosimendan effects is about 1–2 h; the infusion should be continued up to 24 h. Also, inhaled route of administration has been described and claimed to be noninferior compared to the intravenous route (Abdelbaser et al. 2021).

Levosimendan may decrease the mortality rate in adult patients; however, the data in pediatric patients are not enough yet; especially in comparison with milrinone (Mebazaa et al. 2007; Landoni et al. 2012; Lechner et al. 2012; Papp et al. 2012; Nieminen et al. 2013; Li and Hwang 2015; Silvetti et al. 2015; Ferrer-Barba et al. 2016; Kushwah et al. 2016; Rizza et al. 2016; Abril-Molina et al. 2021; Conti et al. 2021; Thorlacius et al. 2021).

Pure Vasodilators

Nitroglycerin

Nitroglycerin (NTG) and nitroprusside are nitric oxide donors (i.e., NO donor); however,

NTG is predominantly a venodilators while nitroprusside is a preferential arterial dilator. Besides, the release of NO after NTG administration is mediated through enzymatic pathways. Venodilation due to NTG leads to a decrease in preload which decreases, in turn, the myocardial wall stress; the final result is improved oxygen balance of the myocardial tissue leading to improved myocardial function. Another beneficial effect of NTG is coronary vasodilation. The therapeutic dose of NTG is 0.5–5 μg/kg/min. However, doses from 0.5 to 2 μg/kg/min lead to venodilation, while doses from 2 to 5 μg/kg/min lead to improved cardiac index and decreased pulmonary and systemic blood pressure. Dose titration is based on clinical response (Hari and Sinha 2011; Divakaran and Loscalzo 2017; Napoli et al. 2019).

Hydralazine

Hydralazine is an antihypertensive drug. It lowers blood pressure with a peripheral vasodilating effect, brought on by interfering with the calcium flow in vascular smooth muscle. Hydralazine effect on peripheral vascular resistance is more pronounced in arterioles (direct arterial dilator) than veins; it decreases diastolic blood pressure more than systolic and leads to an increase in heart rate and stroke volume, and cardiac output. Hydralazine has an increasing effect on renal and cerebral blood flow.

In ***pediatric patients***, hydralazine is used as an oral antihypertensive agent, when BP is not sufficiently controlled by first-line antihypertensive drugs. The common oral dose in hypertension is 0.75 mg/kg daily (or 25 mg/m^2) in four divided doses and can be increased gradually up to 7.5 mg/kg daily (or 200 mg daily). It can also be used parenterally in severe hypertension. In this case, 0.2–0.6 mg/kg hydralazine is administrated IV or IM and can be repeated every 4 hours. Hydralazine is contraindicated in patients with mitral valvular rheumatic heart disease and CAD. However, potential hydralazine side effects are:

- Rebound tachycardia.
- Edema.
- Excessive BP reduction.
- The potential of inducing or exacerbating systemic lupus erythematosus.
- Pyridoxine insufficiency might lead to peripheral neuritis and/or blood dyscrasias; CNS findings and cell blood count should be monitored during treatment.

(Hari and Sinha 2011; Watt et al. 2011; Ostrye et al. 2014; Flynn et al. 2016; Starr and Flynn 2019; Siddiqi and Shatat 2020).

Alprostadil

Alprostadil (prostaglandin E1) has various pharmacologic effects including vasodilation, stimulation of smooth muscle contraction in the intestine and uterus, inhibition of platelet aggregation, and so on. Its vasodilatory effect is shown with doses of 1–10 μg/kg and can reduce blood pressure and reflexes, increase cardiac output and heart rate (Vari et al. 2021).

Since smooth muscles in ductus arteriosus are especially sensitive to alprostadil and based on animal studies, there is evidence that alprostadil can reopen closing ductus in newborns, the drug has been investigated in infants with congenital defects with restricted pulmonary or systemic blood flow who depend on a patent ductus arteriosus for sufficient oxygenation and perfusion.

In such pediatric patients, alprostadil infusion was associated with at least a 10 torr increase in blood PO2 (mean increase about 14 torrs and mean an increase in oxygen saturation about 23%) in about 50% of the patients. Patients with low pretreatment blood PO_2, 4 days old or less, seem to have the best response to alprostadil.

Alprostadil can improve acidosis in patients with restricted systemic blood flow. It can also increase systemic blood pressure, and decrease the ratio of pulmonary artery pressure to aortic pressure.

Alprostadil is administrated as intravenous or intra-arterial infusion and the common dose of this drug in patients with Ductus Arteriosus-dependent Congenital Heart Disease is described here.

In neonates, 0.05–0.1μg/kg/min is the starting dose which can be increased gradually to ≤0.4 μg/kg/ minute. After the therapeutic

response is achieved, the dosage can be reduced for maintenance from 0.1 downward in a stepwise method: 0.05, 0.025, and finally to 0.01 μg/kg/min until the lowest effective dose is achieved. The treatment should be continued until the surgical repair is complete (usually ≤24–48 h). Arterial pressure should be monitored intermittently and the infusion rate should be decreased immediately if the pressure drops significantly. The response can be monitored by measuring blood oxygenation or pH (Carroll et al. 2006; Cuthbert 2011; Strobel and Lu le 2015; Lakshminrusimha et al. 2016; Vari et al. 2021).

Sodium Nitroprusside

Sodium nitroprusside (SNP), similar to nitroglycerin is nitric oxide (NO) donor. Inside the tissues, SNP reacts with physiologic sulfhydryl groups, and the final result is the release of NO which in turn increases tissue levels of cGMP; especially in the arterial and venous system; the final result would be smooth muscle relaxation in the walls of the arterial and venous vessels (Holme and Sharman 2021). Physiologically speaking, SNP decreases afterload of left ventricle leading to improved cardiac output; though some degrees of hypotension occur; however, the improved cardiac output, especially in patients with depressed cardiac function, compensates for the hypotension; unless there is profound preexisting hypovolemia or the patient has underlying obstructive diseases like hypertrophic obstructive cardiomyopathy, aortic stenosis or mitral stenosis (Friederich and Butterworth 1995; Moffett and Price 2008; Thomas et al. 2009; Villarreal et al. 2020).

There is a major concern for SNP toxicity in long-term or large-dose infusions; the reaction of SNP with oxyhemoglobin leads to the formation of methemoglobin; with its final by-product, cyanide anions. Cyanide may be metabolized in the liver, or it could be accumulated in erythrocytes; however, none are greatly toxic. But if cyanide accumulates in the tissues, it could be attached to tissue cytochrome oxidase, which results in toxic impairment of oxidative phosphorylation. To prevent this side effect, we should care about cyanide accumulation and for this purpose, infusion of large doses of the drug for long periods should be prohibited (Moffett and Price 2008; Thomas et al. 2009; Hottinger et al. 2014; Bothof et al. 2020).

The recommended drug dose for intravenous infusion starts at 0.3–0.5 μg/kg/min up to a maximum of 10 μg/kg/min; however, increasing drug dose should be cautiously performed and effect titration should be the basic monitoring tool for increasing the drug dose to prevent hypotension and toxicity. The best predictor for SNP toxicity is its mean dose which predicts elevated cyanide levels better than any other adverse events of cyanide toxicity; especially in postoperative care of pediatric patients undergoing cardiac surgical procedures The onset of action of SNP is within seconds, with its duration to be about 1-2 minutes and its plasma half-life about 3-4 minutes (Varon and Marik 2003; Moffett and Price 2008; Thomas et al. 2009; Moffett et al. 2016; Bothof et al. 2020).

Doses above 3 μg/kg/min, doses more than 48–72 h or in patients with renal insufficiency, the risk of drug toxicity increases significantly. Some studies suggest that in pediatric cardiac surgery, the desired effects of SNP could be gained with 1 μg/kg/min of the drug, and doses above 2 μg/kg/min should be preferably avoided (Friederich and Butterworth 1995; Hottinger et al. 2014; Drover et al. 2015; Holme and Sharman 2021).

Inhalational forms of SNP have been produced to prevent its toxicity especially in patients with pulmonary hypertension.

Phentolamine Mesylate (Regitine)

Phentolamine mesylate is a nonselective alpha-adrenergic blocker of relatively short duration. Its other less pronounced effects include direct positive inotropic and chronotropic effects on cardiac muscle and vasodilator effects on vascular smooth muscle. Blocking the presynaptic α_2-adrenergic receptors can be the cause of tachycardia; however, arrhythmias seen with high doses of Phentolamine decrease the systemic vascular resistance and increase cardiac output. It also reduces pulmonary vascular resistance and pulmonary arterial pressure. The common doses for this drug can be found in Table 6. The most

Table 6 A summary of vasoactive drugs including VASODILATOR and VASOCONSTRICTOR drugs used in congenital heart diseases

Drug	Dose	Receptors	Indication	Half-life (duration)	Adverse effects/notes
Vasopressin	0.01-0.05 U/kg/h	V_1, V_2	Refractory hypotension after conventional drugs have failed, heart failure, vasodilatory shock; e.g., septic shock	10–30 min	Splanchnic ischemia due to its vasoconstrictor action
Phenylephrine	0.02–0.3 μg/kg/min	α_1	Hypotension During Anesthesia	5 min	Nausea, vomiting, headache, nervousness
Nitroglycerin	0.2–10 μg/kg/min	Vascular myocyte/ Guanylyl Cyclase, cGMP ↑	Postcardiac surgery for valvular regurgitation; cardiac surgeries where coronaries are involved, e.g., arterial switch operation, Ross operation and repair for anomalous left coronary artery from a pulmonary artery; and systemic hypertension	1–4 min	Hypotension, tachycardia, methemoglobinemia lead to cyanosis, acidosis, convulsions, and coma
Nitroprusside	0.2–5 μg/kg/min	Vascular myocyte/ Guanylyl Cyclase, cGMP ↑	Systemic hypertension, e.g., after repair of coarctation of the aorta, malignant hypertension of renal vascular origin; acute, severe valvular regurgitation, low cardiac output state following cardiac surgery, especially after valvular surgery, acute heart failure	2 min	Excessive hypotension, cyanide toxicity
Inhaled nitric oxide	10–40 ppm	Vascular myocyte/ cGMP ↑	Pulmonary hypertension of the newborn	2–6 s	Nitric oxide should not be used for the long term, as it results in methemoglobinemia
Prostaglandin E1	0.01 to 0.4 μg/kg/min	Vascular myocyte/ cAMP ↑	In newborns who have congenital heart defects (e.g., pulmonary stenosis, tricuspid atresia) and who depend on patent ductus for survival	0.5–10 min	Hypotension; cardiac arrest; edema
Fenoldopam	0.025–0.3 μg/kg/min Initial dose, titrate to maximum dose 0.8 μg/kg/min	DA-1, α2	Severe hypertension	3–5 min	Hypotension, tachycardia
Nicardipine	1–3 μg/kg/min IV infusion, maximum 15 mg/h	Calcium channel antagonist	Severe hypertension	14.4 h	Headache, hypotension, nausea/vomiting, tachycardia
Phentolamine mesylate	1 mg, 0.1 mg/kg, or 3 mg/m^2	α-adrenergic blocking agent, an imidazoline	Hypertension crisis Hypertension in pheochromocytoma Extravasation of catecholamines Pulmonary artery hypertension	15–30 min	Abdominal pain, nausea, vomiting, diarrhea, exacerbation of peptic ulcer, orthostatic hypotension

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important side effects of this drug are significant sinus tachycardia, arrhythmias, and excessive hypotension (Allen et al. 2013).

Antihypertensive Agents

Hypertension in pediatric patients may lead to organ damage. Currently, a wide range of antihypertensive agents are available in adults and the majority of them could be used in pediatric patients (Flynn 2011; Chu et al. 2014; Dhull et al. 2016; Saini et al. 2021). On the other hand, the treatment of neonatal hypertension is a great challenge and needs sophisticated care (Sharma et al. 2014, 2016).

The current antihypertensive pharmaceutical agents could be categorized mainly in the following subclasses:

Angiotensin-Converting Enzyme (ACE) inhibitors: among them captopril, enalapril, lisinopril, and ramipril are the commonly used agents; however, among other members of the group are fosinopril, perindopril, quinapril, trandolapril, and benazepril that could be mentioned. The main ACE inhibitors are summarized in Table 7 and nearly all of them are safe for the treatment of pediatric hypertension (Chaturvedi et al. 2014a, b; Dhull et al. 2016).

Angiotensin II Receptor Antagonists (ARB's): losartan and valsartan are the prototype drugs in this group; however, other members of the group include: candesartan, eprosartan, irbesartan, olmesartan, and telmisartan. The main ARB's are presented in Table 8. Nearly all ARB's are safe in pediatric patients (Chaturvedi et al. 2014a, b; Dhull et al. 2016).

Calcium Channel Blockers (CCB's): are categorized into two main subgroups including dihydropyridines and nondihydropyridines; these are safe agents for the treatment of pediatric hypertension (Chaturvedi et al. 2014a, b; Dhull et al. 2016). The main CCBs are summarized in Table 9.

Diuretics: diuretic agents are mainly classified into four subgroups which are discussed in Tables 10, 11, and 12 (Dhull et al. 2016; McCammond et al. 2016):

- **Loop** diuretics: (bumetanide, ethacrynic acid, furosemide, torsemide).
- **Potassium-sparing** diuretics (Mineralocorticoid "aldosterone" receptor antagonists): which include spironolactone, amiloride, triamterene.

Table 7 The main ACE inhibitors in pediatric patients

Drug	Dose	Half-life	Adverse effects
Captopril	Oral: 0.3–2.5 mg/kg/d divided every 8–12 h in infants and 0.3–6, mg/kg/d divided every 8–12 h between children and adolescents	Infants: 3.3 h Children: 1–2.3 h	Hypotension Dizziness Headache Rash Hyperkalemia Cough Angioedema
Enalapril	Oral: 0.1–0.5 mg/kg/d divided every 12 h IV (as enalaprilat): 5–10 μg/kg/dose every 8–24 h	Neonates: 10.3 h Infants and children: 2.7 (1.3–6.3) h Enalaprilat: Neonates: 11.9 (5.9–15.6) h Infants and children: 11.1 (5.1–20.8) h	
Lisinopril	Oral: initial: 0.07–0.1 mg/kg/dose once daily ≤0.5–0.6 mg/kg/d	11–13 h	
Ramipril	Oral: 2–6 mg/m^2 daily ≤10 mg daily	Ramiprilat: 13–17 h	

Table 8 The main ARB's used in pediatric patients

Drug	Dose	Half-life	Adverse effects
Losartan	Oral: Initial: 0.5 mg/kg once daily not to exceed Up to 1.4 mg/kg once daily; should not exceed 150 mg/day	1.5–2 h Active metabolite: 6–9 h	Hypotension Dizziness Headache Hyperkalemia Hypoglycemia Diarrhea
Valsartan	1–5 years: oral dose: 0.4–3.4 mg/kg once daily 6–16 years: Initial oral dose: 1.3 mg/kg/dose once daily ≤2.7 mg/kg/dose once daily	4–5 h	

Table 9 The main calcium channel blockers used in pediatric patients

Drug	Dose	Half-life	Adverse effects
Amlodipine	Children 6–17 years: 2.5–5 mg once daily, or divided every 12 h	30–50 h	Edema Dizziness Flushing Palpitations Fatigue Nausea Abdominal pain Somnolence
Nifedipine	Initially, 0.25–0.5 mg/kg daily given in 1 dose or 2 divided doses. up to a maximum dosage of 3 mg/kg (up to 120 mg) daily, given in 1 dose or 2 divided doses	2–7 h	
Isradipine	Initially, 0.15–0.2 mg/kg daily given in 3–4 divided doses. up to a maximum dosage of 0.8 mg/kg (up to 20 mg) daily	Biphasic; initial half-life 1.5–2 h, terminal elimination half-life approximately 8 h	

Table 10 The main loop diuretics

Drug	Dose	Half-life	Adverse effects
Bumetanide	IV, intramuscular, or oral dose: 0.015–0.1 mg/kg/dose every 6–24 h	Neonates: 6 h Infants: 2.4 h	Hyperuricemia Hypomagnesemia Hyponatremia Hypokalemia Metabolic alkalosis
Ethacrynic acid	Oral: 0.5–1 mg/kg/dose every 6–12 h IV: 1–2 mg/kg/dose every 8–12 h	2–4 h	
Furosemide	Oral: 1–2 mg/kg/dose every 6–24 h IV, intramuscular: 0.5–2 mg/kg/dose every 6–24 h Continuous IV infusion: 0.1–0.4 mg/kg/h	0.5–2 h; 9 h in end-stage renal disease	

IV intravenous

Table 11 Spironolactone: the main mineralocorticoid (aldosterone) receptor antagonist

Drug	Dose	Half-life	Adverse effects
Spironolactone	Oral: initial 1 mg/kg/day in divided doses every 6–24 h ≤12.5 to 25 mg/day Maximum: 3.3–6 mg/kg/day divided every 6–24 h; should not exceed 100 mg/day	1.4 h; active metabolites: 12–20 h	Diarrhea Nausea Vomiting Dizziness Hyperkalemia Gynecomastia

Table 12 Thiazide and thiazide-like diuretics

Drug	Dose	Half-life	Adverse effects
Chlorothiazide	Oral: 10–40 mg/kg/day in divided doses every 12 h IV: 4–10 mg/kg/day divided every 12–24 h (maximum 20 mg/kg/day or 500 mg)	45–120 min	Hyperuricemia Hypomagnesemia Hyponatremia Hypokalemia
Hydrochlorothiazide	Oral: 1–4 mg/kg/day in divided doses every 12–24 h	6–15 h	
Metolazone	Oral: 0.2–0.4 mg/kg/day divided every 12–24 h	6–20 h	

- **Thiazide** diuretics: (epitizide, hydrochlorothiazide and chlorothiazide, bendroflumethiazide).
- **Thiazide-like** diuretics: (indapamide, chlorthalidone, metolazone).

Adrenergic receptor antagonists (alpha and/or beta-blockers): some of these agents are discussed under the antiarrhythmic categories; however, some others are presented in Table 13.

Vasodilators: these include arterial and/or venodilators. Nitroglycerin, nitroprusside, hydralazine, and Minoxidil are among common vasodilators. Nitroglycerin and nitroprusside are discussed in the previous parts of the chapter;

Table 13 Some adrenoceptor blocking agents

Drug	Dose	Half-life	Adverse effects
β-blockers			
Metoprolol	Initial oral dose: 0.1–0.25 mg/kg/dose twice daily; not to exceed 12.5–25 mg; up to a maximum daily dose of 1–2 mg/kg/dose twice daily; not to exceed100 mg twice daily	3–4 h (7–9 h in poor CYP2D6 metabolizers)	Brady-arrhythmias Hypotension Headache Dizziness Fatigue
Esmolol	IV Children and adolescents 1–17 years of age: 100–500 μg/kg/min as a constant infusion	4–7 min	The effects due to β1 selective actions
Propranolol	2–4 mg/kg daily in 2 equally divided doses up to 16 mg/kg daily	3–6 h	
Mixed Alpha + Beta-blocker			
Carvedilol	Initial oral dose: 0.1 mg/kg/day divided twice daily Not to exceed 3.125 mg Up to a maximum daily dose of 0.8–1 mg/kg/day; divided twice daily; not to exceed 25 mg twice daily		
Labetalol	Oral Initially, 1–3 mg/kg daily given in 2 divided doses. Maximum: 10–12 mg/kg or 1.2 g daily given in 2 divided doses. IV Injection (Severe Hypertension) Children 1–17 years of age: 0.2–1 mg/kg up to a maximum of 40 mg per dose by direct IV injection, Alternatively, 0.25–3 mg/kg/h by continuous IV infusion	5.5 h after IV administration and 6–8 h after oral administration	The effects due to intrinsic sympathomimetic action, α1 receptor antagonist
Peripheral alpha-blockers			
Prazosin	Initially, 0.05–0.1 mg/kg daily given in 3 divided doses up to 0.5 mg/kg daily in 3 doses	2–4 h	Dizziness Ligh-theadedness Headache Drowsiness Lack of energy Weakness Palpitation Nausea
Terazosin	1–20 mg once daily	Approximately 12 h	
Alpha-2 adrenergic agonists			
Clonidine	Initially, 0.05–0.1 mg, may repeat up to a maximum of 0.8 mg	6–20 h	Dry mouth Dizziness
Methyldopa	Initial oral dose: 10 mg/kg daily given in 2–4 divided doses Intravenous dose: 20–40 mg/kg per day which should be administrated every 6 h; with a max dose of 65 mg/kg or 3 g per day	2–8 h after a single oral dose or 4–12 h multiple oral doses	Drowsiness Sedation Constipation Major depression (for Methyldopa)

Table 14 Common vasodilators used in pediatric patients

Drug	Dose	Half-life	Adverse effects
Hydralazine	Oral 0.75–7.5 mg/kg/day; given in 4 divided doses, max 200 mg/day IM or IV Usual dosage: 1.7–3.5 mg/kg/day or 50–100 mg/m^2/day; which should be given in 4–6 divided doses (Max dose on first dose 20 mg) Severe Hypertension: IV or IM Children and adolescents (1–17 years of age): 0.2–0.6 mg/kg per dose; administer every 4 h when given by intravenous bolus injection	2–4 h	Retention of salt and water Reflex tachycardia Headache Palpitation
Minoxidil	0.25–1 mg/kg/day in 1 or 2 doses up to a maximum dosage of 50 mg/day	4 h	Hypertrichosis Retention of salt and water Nausea and vomiting Pericardial effusion

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while hydralazine and minoxidil are summarized in Table 14. Evidence shows that these agents are applied in the treatment of systemic hypertension in pediatric patients (Hari and Sinha 2011; Ostrye et al. 2014; Dhull et al. 2016; Flynn et al. 2016).

(Driscoll et al. 2015; Xue et al. 2015; Klugman et al. 2016; McCammond et al. 2016; Rossano et al. 2016; Zou et al. 2016)

Drugs Used in Pulmonary Hypertension

For a detailed review on right ventricular failure and pulmonary hypertension treatment, the audience is suggested to refer to chapters "Pulmonary Hypertension" and "Right Ventricular Failure". However, a brief review of the drugs used in pulmonary hypertension in congenital heart surgery is presented in the next paragraphs and Table 15.

The only U.S. Food and Drug Administration (FDA)-approved pharmaceutical specifically for the treatment of pulmonary hypertension in children is inhaled nitric oxide (iNO) which is administered through the lungs. The other FDA-approved drugs for the treatment of pulmonary hypertension used in adults are often based on the pathways related to the endothelial cells, including prostacyclin analogs (epoprostenol, iloprost, treprostinil), Phosphodiesterase 5 inhibitors (sildenafil and tadalafil), phosphodiesterase 3 inhibitors (mainly milrinone), endothelin receptor antagonist (bosentan, ambrisentan, and macitentan), and soluble guanylate cyclase stimulator (riociguat) (Poor and Ventetuolo 2012; Ventetuolo and Klinger 2014; Abman et al. 2015; Jentzer and Mathier 2015; Kim et al. 2016).

Nitric Oxide

Nitric oxide commonly known as NO is a very small lipophilic molecule, with a very crucial role in intracellular signaling mechanisms in many of the cells. NO is synthesized inside the cells from the transformation of L-arginine; nitric oxide synthase (NOS) is the enzyme that catalyzes the production of NO.

When used as an inhaled drug, NO is readily absorbed through the pulmonary system, and after local absorption, produces considerable amounts of cGMP inside the smooth muscle cells; this cellular process leads to smooth muscle relaxation especially in pulmonary blood vessels and subsequently, pulmonary blood pressure drops; the resulting pulmonary vasodilation is a real achievement in the treatment of acute right heart failure especially when weaning from cardiopulmonary bypass is difficult due to pulmonary hypertension or when the patient is in critical pulmonary hypertension crisis and/or acute right heart failure in the intensive care setting.

Table 15 The pharmacological agents used in the management of pulmonary hypertension (Abman et al. 2015; Latus et al. 2015; Hansmann et al. 2016; Kim et al. 2016; Moffett et al. 2016; Aypar et al. 2018; Chen et al. 2018; Li et al. 2019; Wong and Channick 2019; Kuang et al. 2021; Zhao et al. 2021)

Drug	Recommended dose	Adverse effects	Clinical considerations
Inhaled Nitric Oxide (iNO): mechanism of action is increasing cGMP, leading to smooth muscle relaxation and subsequently, pulmonary vasodilation			
iNO	2–5 ppm to a maximum of 40 ppm	Lung injury Increased methemoglobin levels Rebound severe pulmonary hypertension due to abrupt iNO withdrawal	The only FDA-approved agent for pediatric pulmonary hypertension Should not be over administered to prevent side effects Its cost may suggest considering the drug as the last choice
Prostacyclin/Prostacyclin analogs: their mechanism of action is pulmonary and systemic vasodilation through increasing cAMP; also, antiplatelet aggregation			
Epoprostenol	*Initial* infusion rate: 1–3 ng/kg/min *Maintenance* infusion rate: 50–80 ng/kg/min	Flushing, headache, nausea, diarrhea, jaw discomfort, rash, and hypotension, thrombocytopenia	The potential risk of hypotension and bleeding in children receiving drugs, such as anticoagulants, platelet inhibitors, or other vasodilators
Iloprost	*Initial* dose: 2.5 μg per inhalation; 6 times/day *Maintenance* dose: 5 μg per inhalation 9 times/day	Cough, wheeze, headache, flushing, jaw pain, diarrhea, rash, and hypotension (at higher doses)	The potential risk of exacerbation of reactive airway disease
Treprostinil (IV/subcutaneous)	*Initial* infusion rate: 1.25–2 ng/kg/min *Maintenance* infusion rate: 50–80 ng/kg/min	Flushing, headache, nausea, diarrhea, musculoskeletal discomfort, rash, hypotension, thrombocytopenia, and pain at the subcutaneous infusion site	Similar to epoprostenol
Treprostinil (inhaled)	*Initial* dose: 3 breaths (18 μg)/4 times/day *Maintenance* dose: 9 breaths (54 μg) 4 times/day	Cough, headache, nausea, dizziness, flushing, and throat irritation	Reactive airway symptoms and hypotension may occur at high doses
Treprostinil (oral)	*Initial* dose: 0.25 mg PO BID *Maintenance* dose: determined by tolerability	Headache, nausea, diarrhea, jaw pain, extremity pain, hypokalemia, abdominal discomfort, and flushing	If "twice daily" dosing is not tolerated, consider "three times daily" dosing
PDE-5 inhibitors: inhibit phosphodiesterase-5, leading to pulmonary vasodilation and inhibition of the vascular remodeling			
Sildenafil	*Oral* dose: 0.25–0.5 mg/kg/q4–8 h *Intravenous* dose: loading dose 0.4 mg/kg over 3 h Maintenance: continuous infusion of 1.5 mg/kg/day	Headache, flushing, rhinitis, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, and back pain	Co-administration of nitrates is contraindicated Sensorineural hearing loss and ischemic optic neuropathy have been reported
Tadalafil	Oral dose: 1 mg/kg per day (single daily dose): preliminary studies	Similar to sildenafil No significant effect on vision	Similar to sildenafil

(continued)

Table 15 (continued)

Drug	Recommended dose	Adverse effects	Clinical considerations
Antagonists of Endothelin Receptor: counteract with the effects of both endothelin receptors (ET_A and ET_B), vasodilation of the pulmonary vascular system, and vascular remodeling inhibition			
Ambrisentan	Body weight < 20 kg: 2.5–5 mg PO/4 times daily Bodyweight >20 kg: 5–10 mg PO/4 times daily	Peripheral edema, nasal congestion, headache, flushing, anemia, nausea, and decreased sperm count	Baseline liver enzymes and hemoglobin are needed Monitor based on clinical parameters
Bosentan	2 mg/kg per dose PO, two times daily If bodyweight is 10–20 kg: 31.25 mg PO, two times daily If bodyweight is 20–40 kg: 62.5 mg PO, two times daily If bodyweight is >40 kg: 125 mg PO two times daily	Pediatric Abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, edema, nasal congestion, anemia, and decreased sperm count The potential risk of dose-dependent increases in amino-transaminase levels	Liver enzymes and hemoglobin levels should be monitored; in patients with moderate or severe degrees of hepatic impairment, should be used cautiously Also, concomitant use of CYP3A4 inducers and inhibitors should be considered as an important caution
Macitentan	10 mg PO, four times daily	Nasal congestion, headache, flushing, anemia, and decreased sperm count	The incidence of serum aminotransferase elevation is low Obtain baseline liver enzymes and hemoglobin; monitor as clinically indicated Teratogenicity REMS
sGC stimulator: its action mechanism is stimulation of soluble guanylate cyclase leading to pulmonary vasodilation associated with inhibition of the vascular remodeling			
Riociguat	*Initial* dose: 0.5–1 mg PO *Maintenance* dose: 2.5 mg PO, three times daily	Headache, dizziness, dyspepsia, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation	Co-administration of nitrates and/or PDE-5 inhibitors is contraindicated In growing rats, effects on bone formation were observed Teratogenicity is a potential risk Visit www.adempasREMS.com

The molecules of NO when administered through the pulmonary route are called inhaled NO (briefly iNO). iNO is transported very fast through the alveolar-capillary membranes and then, its molecules are rapidly metabolized by circulating erythrocytes. This rapid process of absorption and metabolism takes just a few seconds and so, makes iNO an ideal drug; the inhalational route is among the best appropriate targeted therapies in pulmonary hypertension which act exactly on the specific site of action (pulmonary vascular system) while there are the least possible systemic side effects (Kim et al. 2016; Moffett et al. 2016).

Dose: iNO is administered through the endotracheal tube, face mask, or nasal cannula. It is started with the lowest possible doses, from 2 to 5 ppm to a maximum of 40 ppm; higher doses are both ineffective and may cause side effects. iNO needs specific delivery instruments, its costs are high, and very high doses may lead to lung injury and/or increased methemoglobin levels, mandating routine monitoring of methemoglobin levels. iNO should ***not*** be withdrawn abruptly, or there would be severe rebound pulmonary hypertension (Atz and Wessel 1997; Mossad 2001; Gao and Raj 2010; Pritts and Pearl 2010; Abman et al. 2015; Latus et al. 2015; Hansmann et al. 2016; Kim et al. 2016; Moffett et al. 2016).

Phosphodiesterase 5 (PDE 5) inhibitors include sildenafil, tadalafil, and vardenafil; among them, sildenafil and tadalafil are the most commonly used agents for pulmonary hypertension.

Sildenafil

Sildenafil is one of the classes of drugs known as phosphodiesterase 5 (PDE 5) inhibitors. PDE 5 degrades cGMP and when it is inhibited by sildenafil, accumulation of PDE 5 in smooth muscles of the pulmonary system leads to pulmonary vasodilation and improves pulmonary hypertension, both in acute and chronic pulmonary hypertension. It is available both in oral and intravenous forms. However, its use should be associated with extreme caution especially in critical patients to prevent any potential life-threatening hypotension. In European Union, sildenafil has approval for the treatment of pediatric patients between 1 and 17 years. However, in the US, there are still some concerns regarding the safety of sildenafil in pediatric pulmonary hypertension, especially for high doses of sildenafil and also, for its application in term and preterm infants, when iNO is available. That means, currently iNO is the only formally approved agent for the treatment of pulmonary hypertension in infants and neonates with pulmonary hypertension in the US, while sildenafil is used in other places for the same indication. The recommended oral dose of sildenafil is 0.25–0.5 mg/kg each 4–8 h, with a maximum dose of 2 mg/kg every 4 h; titration of the dose should be based on clinical response; intravenous dose could be found in Table 15. These data are in large the same for tadalafil; the only difference is the dose of tadalafil; the dosage of tadalafil could be found in Table 14 (Shah and Ohlsson 2011; Beghetti et al. 2014; Vorhies and Ivy 2014; Wang et al. 2014; Dodgen and Hill 2015; Perez and Laughon 2015; Lakshminrusimha et al. 2016).

Endothelin Receptor Blockers (ET Blockers)

Endothelin receptor antagonists block endothelin receptors on endothelium and vascular smooth muscle (stimulation of these receptors is associated with vasoconstriction).

Bosentan, an endothelin receptor antagonist, can inhibit both ET_A and ET_B receptor activities, with a slightly higher affinity for the A subtype; therefore it lowers pulmonary artery pressure (PAP) and pulmonary vascular resistance (PVR) and improves exercise tolerance in adults with pulmonary arterial hypertension. The same results are well established in children and adults diagnosed with congenital heart diseases with pulmonary hypertension especially in the short-term use of the drug, as clinical improvement in "6-minute walk distance (6MWD) and the World Health Organization functional class (WHO-FC)" (Guo et al. 2014; Herbert et al. 2017; Kuang et al. 2018; Li et al. 2019; Wong and Channick 2019; Kuang et al. 2021). Liver function tests should be monitored due to the possibility of hepatotoxicity (Chen et al. 2018). Other potential adverse effects of bosentan include headache, flushing, lower limb edema, hypotension, palpitations, dyspep-

sia, and anemia (Allen et al. 2013; Kuang et al. 2021).

The common dosing for bosentan is as follows:

- 10–20 kg: Initial: 31.25 mg once daily for 4 weeks; increase to the maintenance dose of 31.25 mg twice daily.
- >20–40 kg: Initial: 31.25 mg twice daily for 4 weeks; increase to the maintenance dose of 62.5 mg twice daily.
- >40 kg: Initial: 62.5 mg twice daily for 4 weeks; increase to the maintenance dose of 125 mg twice daily.

Ambrisentan, the other member of the family, affects as a selective agent for the type A endothelin receptors (ETA), while it is similar to bosentan in efficacy (Patel et al. 2018; Zhao et al. 2021). For other data, see Table 15.

Macicentan, the third member of the family, acts as a dual endothelin receptor antagonist (against both A and B subtypes of endothelin receptor; ETA and ETB) has been approved in 2013 for the treatment of pulmonary arterial hypertension with 50-fold increased selectivity for the ETA subtype than ETB; its main advantages are "fewer contraindications, applicability in impaired hepatic function, and administration as a once-daily tablet" (Bruderer et al. 2012; Hong et al. 2014; Aypar et al. 2018). For other data,, see Table 15.

Safety monitoring: in patients treated with ET-1 antagonists, safety monitoring of the organ functions should be considered as below (Liu et al. 2013; Herbert et al. 2017; Aypar et al. 2018; Chen et al. 2018; Li et al. 2019; Wong and Channick 2019; Kuang et al. 2021; Zhao et al. 2021):

- Bosentan: careful monitoring of the liver function.
- Ambrisentan: chance of peripheral edema; while it has a better profile regarding liver function.
- Macitentan: chance of anemia and peripheral edema.

Milrinone

Milrinone is discussed in previous sections under "inodilators".

Antiarrhythmic Agents

The antiarrhythmic agents are based on the following classification which is known as Vaughan Williams Classification of Antiarrhythmic Agents. This classification depends mainly on the cellular physiology of myocardial cells, discussed fully in chapter "Pediatric Cardiovascular Physiology". A schematic picture of the myocardial action potential is demonstrated here which helps understand the mechanism of these agents (Fig. 1). The Vaughan Williams Classification of Antiarrhythmic Agents is described in brief in Table 16. Also, detailed descriptions of selected agents are described in Table 17 (Moffett et al. 2016; Dan et al. 2018; Lei et al. 2018).

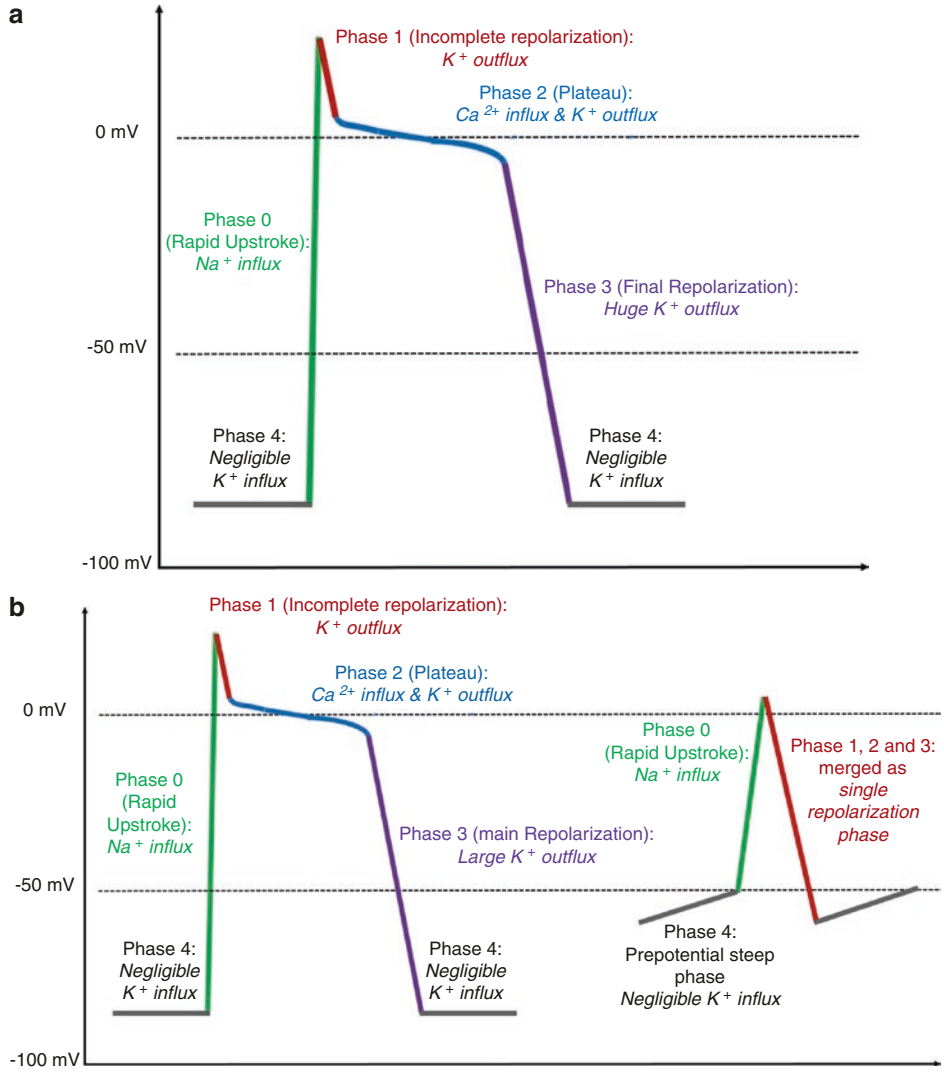

Fig. 1 (**a**) Progress of Action Potential Phases in normal myocardial cells; (**b**) Comparison of Action Potential Phases between normal myocardial cells and pacemaker cells (Marcotti et al. 2004; Parham et al. 2006; Wolf and Berul 2008; Amanfu and Saucerman 2011; Marionneau and Abriel 2015; Dabbagh et al. 2019)

Table 16 Vaughan Williams classification of antiarrhythmic agents (Vaughan Williams 1989, 1992; Zipes et al. 2006; Moffett et al. 2016; Dan et al. 2018; Lei et al. 2018; Bos et al. 2019; Lavalle et al. 2021; Yang et al. 2021)

Class of drugs	Mechanism of action	Drugs (alphabetic order)
Class I a	**Fast Na channel blockers:** depress phase 0, prolonging repolarization	Disopyramide, procainamide, quinidine
Class Ib	**Fast Na channel blockers:** selectively depress phase 0 in abnormal/ischemic tissue, shorten repolarization	Lidocaine, mexiletine, phenytoin, tocainide
Class Ic	**Fast Na channel blockers:** markedly depress phase 0, with minimal effect on repolarization	Flecainide, moricizine, propafenone
Class II	Beta-blockers: decreases slope of phase 4	Atenolol, bisoprolol, carvedilol, esmolol, metoprolol, propranolol, timolol
Class III	Potassium (K) channel blockers that prolong the cardiac action potential: mainly prolong phase 3	Amiodarone, dofetilide, Ibutilide, sotalol
Class IV	Slow calcium (Ca) channel blockers: prolong phase 2	Diltiazem, verapamil
Class V	Variable mechanism	Adenosine, digoxin, magnesium sulfate

Table 17 Individual anti-arrhythmic agents (Moffett et al. 2016; Dan et al. 2018; Lei et al. 2018; Bos et al. 2019; King et al. 2021; Lavalle et al. 2021; Pannone et al. 2021; Yang et al. 2021)

Medication	Dosing	Indication	Adverse events	Specific clinical considerations
Class I a				
Procainamide	IV loading dose: 3–6 mg/kg per dose; Maximum dose: 100 mg per dose (total maximum dose: 15 mg/kg) IV: continuous infusion: 20–80 μg/kg/min	Atrial tachycardia; JET; VT	Hypotension and pro-arrhythmia	Procainamide and NAPA concentrations are used as serum markers of therapy
Disopyramide	<1 year of age 10–30 mg/kg 1–4 years of age: 10–20 mg/kg 4–12 years of age: 10–15 mg/kg 12–18 years of age: 6–15 mg/kg	Ventricular arrhythmias	Anticholinergic effects	It may be ineffective in patients with hypokalemia and toxic effects may be enhanced in patients with hyperkalemia
Quinidine	Oral dose: 30 mg/kg/day or 900 mg/m^2/day given in five daily doses Range: 15–60 mg/kg/day in four or five divided doses IV dose: 2–10 mg/kg per dose every 3–6 h as needed	SVT, VT, Atrial tachycardia ventricular premature complexes	Hypotension (particularly with IV formulation)	Drug level monitoring is typically not performed There are two forms of drug available (sulfate and gluconate) IV route is not routinely recommended because of hypotension
Class I b				
Lidocaine	IV bolus: 1 mg/kg per dose IV continuous infusion: 20–50 μg/kg/min	PVCs, VT, VF	Hypotension and numbness	
Mexiletine	Adults: 400-mg loading dose (in rapid control) followed by 200 mg in 8 h	Ventricular arrhythmias	development or exacerbation of arrhythmias and hypotension	Limit use to those with life-threatening arrhythmias, lack evidence for improved survival for class I antiarrhythmic agents
Phenytoin	Adults: Oral 100 mg 2–4 times daily IV 100 mg by direct IV injection at 5-min intervals until a total of 1 g is given	VT, PAT	Hypotension, severe cardiotoxic reactions (e.g., decreased cardiac output, atrial or ventricular conduction depression, ventricular depression	IV use contraindicated in patients with sinus bradycardia, SA block, second- or third-degree AV block, or Adams-Stokes syndrome
Tocainide: no longer sold in the US				
Class I c				
Flecainide	Oral: starting dose: 1–3 mg/kg/day or 50–100 mg/m^2/day Maximum oral dose: 8 mg/kg/day or 200 mg/m^2/day divided by three times/day	SVT	Potential for pro-arrhythmia in patients with congenital heart disease	Caution use in patients with congenital heart disease; milk feeds may decrease absorption; level monitoring may assist in guiding therapy

Moricizine: withdrawn from the market				
Propafenone	Oral: 200–300 mg/m^2/d (max: 600 mg/m^2/d) divided three or four times/d	Paroxysmal atrial fibrillation/flutter and paroxysmal supraventricular tachyarrhythmias, VT, atrial fibrillation	Bradycardia and pro-arrhythmia	
Class II (beta-blockers)				
Atenolol	Oral: 0.5–1 mg/kg/d given one or two times/d (max: 2 mg/kg/d or 100 mg/d)	SVT, VT	Bradycardia, hypotension, and hypoglycemia	
Bisoprolol: no indication as an antiarrhythmic agent				
Carvedilol: no indication as an antiarrhythmic agent				
Esmolol	IV: bolus: 100–500 µg/kg per dose IV: continuous infusion: 300–1000 µg/kg/min	Sinus tachycardia; atrial and ventricular tachyarrhythmias	Bradycardia, hypotension, and hypoglycemia	
Metoprolol	Oral: children 1–17 years: 1–2 mg/kg/d given twice daily (max: 6 mg/kg/day or 200 mg/day)	SVT, VT	Bradycardia, hypotension, and hypoglycemia	
Propranolol	Oral: neonates: 0.25 mg/kg per dose every 6 h (max: 5 mg/kg/d) Oral: infants and children: 0.5–1 mg/kg/d in divided doses every 6–8 h (max: 60 mg/d)	SVT, VT	Bradycardia, hypotension, and hypoglycemia	
Timolol: no indication as an antiarrhythmic agent				
Class III				
Amiodarone	IV: bolus: 5 mg/kg per dose up to 15 mg/kg IV: continuous infusion: 10–20 mg/kg/d or 5–15 µg/kg/min Oral: 10–20 mg/kg/d or 600–800 mg/m^2/d one or two times/d	Atrial tachycardia, flutter, and fibrillation; JET; VT and VF	Bradycardia, hypotension, Torsade de Pointes, hepatotoxicity, thyroid dysfunction, skin color alteration, corneal deposits, and pulmonary fibrosis	Patients may require 1–2 weeks of loading dose (higher doses) at the beginning of therapy due to the long half-life of amiodarone Extensive laboratory monitoring at baseline required due to high incidence of adverse events

(continued)

Table 17 (continued)

Medication	Dosing	Indication	Adverse events	Specific clinical considerations
Dofetilide	Adults: Initially, 500 μg twice daily; modify dosage according to Clcr and QTc interval	SVT	Arrhythmias (torsade de pointes)	Arrhythmogenic, contraindicated in congenital or acquired long QT syndromes; baseline QT or QTc interval >440 ms (500 ms in patients with ventricular conduction abnormalities) Severe renal impairment (calculated Clcr <20 mL/min)
Ibutilide	***Atrial Flutter and/or Fibrillation*** IV **Adults** weighing ≥60 kg: Initially, 1 or 2 mg Adults weighing <60 kg: Initially, 0.01 mg/kg (10 μg/kg) Repeat after 10 min if needed ***Atrial Flutter and/or Fibrillation following Coronary Bypass Graft or Valvular Surgery*** IV Adults weighing ≥60 kg: 1 or 2 infusions of 0.5 mg each (given 10 min apart) Adults weighing <60 kg: 1 or 2 infusions of 0.005 mg/kg (5 μg/kg) each (given 10 min apart)	SVT, atrial flutter and/or fibrillation following coronary bypass graft or valvular surgery	Arrhythmia, CHF, renal failure	Atrial arrhythmias of not so recent onset are less likely to respond to the drug. Efficacy not determined in atrial arrhythmias of >90 days' duration (AHFS 2016)
Sotalol	Oral: children ≤2 years: 30 mg/m^2 per dose every 8 h adjusted per age nomogram or 2 mg/kg/d divided every 8 h or 80–200 mg/m^2/d divided every 8 h Oral: children >2 years: 80–200 mg/m^2 per dose divided every 8 h	Atrial Arrhythmia, VT	Bradycardia, hypotension, hypoglycemia, and Torsade de Pointes	Dosing for infants <2 years is controversial; ECG monitoring for QT prolongation necessary; women at greater risk for TdP than men

Class IV				
Diltiazem	Adults: IV Initially, 15–20 mg (or 0.25 mg/kg) by direct IV injection over 2 min. 20–25 mg (or 0.35 mg/kg) can be administrated 15 min after the initial if needed Maintenance infusion: 5–15 mg/h; titrate dose to heart rate	SVT	Hypotension, renal or hepatic injury, slowing cardiac conduction, possible transient VPB on the conversion of PSVT to sinus rhythm	IV diltiazem contraindicated • In patients with VT • Patients with atrial flutter or fibrillation with an accessory pathway • If concurrent or recent (e.g., within a few hours) administration of IV β-adrenergic blockers
Verapamil	IV: children 1–15 years: 0.1–0.3 mg/kg per dose; max, 5 mg per dose Oral: 4–8 mg/kg/d in three divided doses or 1–5 years: 40–80 mg every 8 h and >5 years: 80 mg every 6–8 h	SVT	Hypotension and bradycardia	IV use is not recommended in patients who are <1 years old because of the risk of cardiovascular collapse
Class V				
Adenosine	IV: 0.1 mg/kg per dose; subsequent doses, 0.2 mg/kg per dose, up to 0.3 mg/kg per dose	SVT	Gasping, chest pain, flushing, and wide complex tachycardia	Rapid flush required immediately after adenosine infusion; should be given at a site closest to the heart Life support equipment should be nearby when administering adenosine
Digoxin	Oral and IV: loading doses and maintenance doses have considerable variation depending on age and range from 5 to 50 μg/kg per the dose given in three divided doses. Historically, oral maintenance doses have ranged from 5 to 10 μg/kg/d divided twice daily	Atrial fibrillation and flutter, sinus tachycardia, paroxysmal supraventricular tachycardias	Bradycardia, nausea/vomiting, and visual disturbances	Adverse events from digoxin toxicity may occur in patients with kidney dysfunction, electrolyte disturbances, or drug interactions
Magnesium sulfate	IV: 25–50 mg/kg per dose infusion for Torsade de Pointes	VT (Torsade de pointes) Prevention of JET	Hypotension, muscle weakness, sedation	May cause hypotension on infusion; rate of infusion should be dictated by patient condition

IV intravenous, *SVT* supraventricular tachycardia, *AV* atrioventricular, *JET* junctional ectopic tachycardia, *VT* ventricular tachycardia, *VF* ventricular fibrillation, *PVC* premature ventricular contraction

Analgesic Agents, Sedative Drugs, and Intravenous Anesthetic Agents

Analgesia is one of the most mandatory needs during the perioperative period in pediatric cardiac surgery. The children are threatened when they are separated from their parents. Even, for routine visits, anxiety and fear may disturb the child. Add to this, the pain due to surgical procedures, suffering from procedures like tracheal suctioning, chest tube manipulations, and dressing change (Lucas et al. 2016).

Clinical assessment of pain and sedation level is among the most basic skills needed in the perioperative period. A full description of these tools and skills is described in chapter "Central Nervous System Monitoring in Pediatric Cardiac Surgery". However, to just mention the titles, the most commonly used sedation scales in these settings are:

- Ramsay Sedation Scale (Ramsay).
- Sedation Agitation Scale (SAS).
- Richmond Agitation Sedation Scale (RASS).

The very low cardiorespiratory reserve of children and infants with congenital heart diseases makes perioperative sedation and analgesia a great challenge for the caregivers that need sophisticated vigilance and exact monitoring. Overtreatment and under-treatment both have their problems. Also, in the current era of fast-track extubation, real-time continuous monitoring is the cornerstone of postoperative care for congenital heart disease patients. These mandate appropriate choice of analgesic/sedative agents. And if the patient is going to be mechanically ventilated due to any underlying problem including hemodynamic instability, use of assist devices, pulmonary insufficiencies, or CNS insults, careful use of muscle relaxants is often among the needed ingredients of the sedation/analgesia care. Volatile anesthetics, though are not usual in postoperative care, have a crucial role in the operating room and also could be used for some procedures (including but not limited to using sevoflurane for echocardiography in a restless baby). Tables 18, 19, 20, and 21 describe in brief, the most common analgesics, sedatives, muscle relaxants, and anesthetic gases used in the perioperative care of patients with congenital heart disease (Friesen and Williams 2008; Verghese and Hannallah 2010; Galante 2011; Twite and Friesen 2014; Lucas et al. 2016; Maldifassi et al. 2016).

Drugs for Pediatric Delirium

Postoperative delirium after pediatric cardiac surgery is a challenging issue; the current recommendations are based on consensus than pure evidence. So, there are at times some extrapolations from adult cardiac surgery to pediatric cardiac surgery; for example, benzodiazepines are not recommended for the treatment of postoperative delirium after pediatric cardiac surgery because these drugs are potentially deliriogenic in adult patients.

The consensus is that if nonpharmacological treatments of delirium and agitation go unsuccessful, pharmacological treatment should be started to prevent the child from discomforting or endangering himself/herself; in other words, a delirious child interferes with the treatment process while a well-treated child opens "appropriate environment" for the parents to take part in the process of care; also, a delirious child increases the risk of unplanned events like unwanted endotracheal extubation, failure of any vascular lines like intravenous lines, the arterial line, or central venous line and adds the risk of unwanted physical trauma to the patient (Malarbi et al. 2011).

In general, appropriate pharmacological treatment of a delirious child in the postoperative period of cardiac surgery improves the overall course of treatment; so, pediatric delirium when recognized responds well to treatment (Schieveld et al. 2007; Madden et al. 2011; Hipp and Ely 2012).

Treatment of hyperactive delirium should be based on some principles:

- Some of the pharmacologic agents have delirium preventing effects; for example, premedication with clonidine (4 μg/kg), propofol, ketamine, halothane, dexmedetomidine, or opioids (e.g., fentanyl) has possible prophylac-

Table 18 Analgesic agents (opioids and nonopioids)

Medication	Dosing	Indication	Adverse events and specific clinical considerations
Fentanyl (Opioid)	Bolus: 1–2 μg/kg Infusion: 1–10 μg/kg/h **Transdermal** fentanyl patches are available but should be avoided in children <2 years due to thin stratum corneum of the skin and increased body surface area ratio which enhance transdermal absorption	Analgesia	Chest wall rigidity with rapid bolus or high doses; rapid tolerance with infusion, respiratory depression, depressed consciousness, hallucinations, hypotension, nausea/vomiting, decreased GI motility/ileus, urinary retention Withdrawal symptoms when moderate to high doses are used for up to or more than one week Preferred for a rapid onset of analgesia in acutely distressed patients Individualize dose for each patient Virtually devoid of histamine-releasing properties More rapid onset of action and a shorter half-life than morphine Renal failure does not appear to largely affect the pharmacokinetics Onset: 30 s Duration: 30–45 min
Remifentanil (Opioid)	Bolus:1–3 μg/kg/dose Infusion (preferred):0.4–1 μg/kg/min	Analgesia	Half-life: 10-15 min, has been associated with bradycardia and hypotension particularly during rapid infusion Has no liver or renal elimination
Morphine (Opioid)	Bolus: 0.05–0.1 mg/kg Infusion: 0.025–0.1 mg/kg/h Single dose: 0.1 mg/kg	Analgesia	Peak: 20 min Respiratory depression, depressed consciousness, hallucinations, hypotension, nausea/vomiting, decreased GI motility/ileus, urinary retention, histamine release: flushing, tachycardia, pruritus may occur Withdrawal symptoms when moderate to high doses are used for up to or more than 1 week
Methadone (Opioid)	0.1–0.2 mg/kg q 8–12 h	Analgesia; opioid tolerance	Use for opioid wean protocol
Hydromorphone	**Oral**: 0.03–0.08 mg/kg/dose q 4 h **Single IV** dose: 0.01–0.02 mg/kg q 4 h **Continuous IV** infusions: 1 μg/kg/h Titration parameter: Pain scale	Analgesia	Respiratory depression, depressed consciousness, hallucinations, hypotension, nausea/vomiting, decreased GI motility/ileus, urinary retention Individualize dose for each patient Available as PCA The effect of renal insufficiency on the elimination of hydromorphone is unknown More rapid onset of action and a shorter half-life than morphine Withdrawal symptoms when moderate to high doses are used for up to or more than 1 week
Acetaminophen (nonopioid: inhibits prostaglandin synthesis)	10–15 mg/kg q 6 h	Nonopioid analgesia	Do not use when there is a significant hepatic disease
Ketorolac (nonopioid: Nonsteroidal anti-inflammatory agent (cyclooxygenase-1 and 2 inhibitor)	0.5 mg/kg q 6 h; max 30 mg; do not administer for more than 48–72 h	Nonopioid analgesia	Injection site pain, abdominal pain, constipation, diarrhea, flatulence, indigestion, nausea/vomiting, headache Inhibition of platelet function: may cause bleeding Use with caution in patients with preexisting renal insufficiency Use the lowest effective dose for the shortest period

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Table 19 Sedative drugs and intravenous anesthetics (Friesen and Williams 2008; Verghese and Hannallah 2010; Galante 2011; Twite and Friesen 2014; Lucas et al. 2016; Maldifassi et al. 2016; Ronaghi et al. 2016; Behnaz et al. 2020; Hosseini et al. 2020; Moshari et al. 2020; Mirkheshti 2021)

Medication	Mechanism of action	Dosing	Indication	Adverse events and specific clinical considerations
Propofol	Modulation of $GABA_A$ receptor complex	Bolus: 1–3 mg/kg Infusion: 100–200 μg/kg/min for procedural sedation	Procedural sedation	Do not use for prolonged ICU sedation, i.e., >4 h (risk of Propofol infusion syndrome)
Midazolam	Modulation of $GABA_A$ receptor complex	Infusion: 0.025–0.1 mg/kg/hour average: 0.05–0.1 mg/kg/h	Amnesia, sedation, anxiolysis	Rapid tolerance with the infusion Onset: 1–5 min Duration: 20–30 min
Lorazepam	Modulation of $GABA_A$ receptor complex	Bolus: 0.025–0.1 mg/kg q 4 h Infusion:0.025 mg/kg/hr	Amnesia, sedation, anxiolysis	Risk of tolerance with the infusion Onset: 1–5 min Duration: 20–30 min
Dexmedetomidine	Synthetic central α2 agonist (purely α2; vs. clonidine)	0.3–0.7 μg/kg/h	Sedation; some analgesia	For short-term ICU sedation; bradycardia and heart block in infants half-life: 6–12 min
Clonidine	α1 and α2 adrenoceptor agonist (90% α2 with some α1 activity)	Infusion: 0.25–1 μg/kg/hr	Analgesia, sedation	Does not cause significant respiratory depression May lead to hypotension
Etomidate	Modulation of $GABA_A$ receptor complex	Children >10 years of age: 0.3 mg/kg (0.2–0.6 mg/kg)	Sedation	Onset: 1 min Duration: 3–5 min
Ketamine	NMDA receptor antagonist	Bolus: 1.5–2 mg/kg May administer incremental doses of 0.5 to 1 mg/kg every 5 to 15 min as needed	Analgesia, sedation	Hallucinations, dysphoria, excessive salivation, tachycardia onset: 3–5 min duration: 20–30 min

tic effects in prevention of delirium or decreasing the chance and/or severity of postoperative delirium in children undergoing general anesthesia (Dahmani et al. 2010; Costi et al. 2014; Lambert et al. 2014; van Hoff et al. 2015).

- On the other hand, there might be an increased occurrence of delirium after anesthesia with some gases like sevoflurane especially when the patient is not premedicated (Messieha 2013).
- Pharmacologic treatment, when started, should be continued until the clinical signs persist, or until any risk factor for delirium continues to exist; also, after healing, pharmacologic agents should not be abruptly "turned off"; instead gradual tapering and drug weaning are the preferred route.
- Intravenous haloperidol and oral risperidone are the main drugs used for pharmacologic treatment, which is the common route for many critical patients; however, adverse events of risperidone are less than haloperidol (Warshaw and Mechlin 2009; Powney et al. 2012).
- Risperidone does not have an intravenous form, but its oral form is available and is the preferred choice whenever it is possible to use oral medication and symptoms are not severe; also, in the first opportunity, haloperidol should be replaced with risperidone to decrease the chance of adverse events of haloperidol (Madden et al. 2011; McPheeters et al. 2011).
- Routine delirium scoring, at least three times a day, should be done as long as pharmacologic treatment is continued (van Dijk et al. 2012).
- Adverse events pharmacologic treatment is especially seen when escalating doses are

Table 20 Volatile anesthetics

Drug	MAC value %	Comments
Isoflurane	1.6 (newborn) 1.87 (1–6 months) 1.8 (0.5–1 year) 1.6 (1–12 years)	Irritates the respiratory tract, which may lead to laryngospasm in children
Sevoflurane	3.3 (newborn) 3.1 (1–6 months) 2.7 (0.5–1 years) 2.55 (1–12 years)	A good choice for mask induction in pediatric anesthesia Decreases the chance of postoperative nausea and vomiting Shortened recovery time and more rapid recovery of perception, which might produce a state of restlessness
Desflurane	9.2 (newborn) 9.4 (1–6 months) 9.9 (0.5-1 years) 8.0 to 8.7 (1-12 years)	Not suitable for mask induction in pediatric anesthesia because of its pungent smell, respiratory tract irritation, apnea, and laryngospasm
Xenon	71	When a mixture of 30 volume% oxygen and 70 volume% xenon is used, the analgesic effect is excellent Extremely costly Increases pulmonary artery pressure
Nitrous Oxide	105, so could never be a sole anesthetic agent	Not widely used in cardiac surgery and ***should not be used*** on newborns and children with pulmonary infections In combination with other agents, reduces the need for volatile anesthetics ***Should not be used*** on newborns and children with pulmonary infections
Enflurane	1.7 (1–12 years) 1.6 (adult)	Not used in pediatric anesthesia due to possible epileptic effects and the possibility of raising hepatic enzymes
Halothane	0.87 (newborn) 1.2 (1–6 months) 0.97 (0.5–1 year) 0.89 (1–12 years)	Side-effect: increased sensitivity of myocardium to circulating catecholamines. A rise in hepatic enzymes May lead to increased occurrences of intra-operative arrhythmia

MAC minimum alveolar concentration
(Friesen and Williams 2008; Verghese and Hannallah 2010; Galante 2011; Dabbagh and Rajaei 2012; Twite and Friesen 2014; Lucas et al. 2016; Maldifassi et al. 2016)

increased suddenly and abruptly; instead, gradual commencement of the drug and gradual weaning after the termination of the clinical signs is the preferred method.

- The main complications of pharmacologic treatment with antipsychotics include extrapyramidal symptoms and long QTc interval.
- Extrapyramidal symptoms (including dystonia, akathisia, hyperpyrexia) should be monitored and treated with anticholinergics like biperiden with a dose of 50 μg/kg which is administered slowly through an intravenous line; also, the dose of antipsychotics should be reduced (Satterthwaite et al. 2008).
- Another main complication is the lengthening of QTc interval which might lead to lethal Torsade de Pointes; performing ECG monitoring and recording the results for more comparisons are a need that should be fulfilled before, during, and after antipsychotic treatment (Brahmbhatt and Whitgob 2016).

A detailed list of drugs used for the treatment of pediatric ICU delirium are presented in Table 22 and its data are based on the recent advances related to pharmacotherapy of postoperative delirium (Schieveld et al. 2007, 2009; Maglione et al. 2011; Loy et al. 2012; Asmal et al. 2013; Baron et al. 2015; Joyce et al. 2015; Masi et al. 2015; Smith et al. 2016).

Stress Ulcer Prevention and Treatment

In postoperative pediatric patients, the chance for postoperative stress ulcers is always a real potential threat (Griffin 1998; Langford and Mehta 2006). Pharmacologic therapy in pediatric patients though considered by many is still used for many of the drugs in pediatric perioperative care as off-label use; still, there is a paucity of data regarding high-quality evidence for the

Table 21 Neuromuscular blocking agents (depolarizing; nondepolarizing)

	Succinylcholine	Pancuronium	Vecuronium	Cisatracurium	Atracurium	Rocuronium
Initial dose	1–2 mg/kg	0.06–0.15 mg/kg	0.08–0.1 mg/kg	0.1–0.15 mg/kg	0.4–0.5 mg/kg (0.3 to 0.4 mg/kg for 1 month to 2 years of age)	0.6–1.2 mg/kg
Onset of effect	<1 min	2–5 min	1–3 min	1–3 min	1–3 min	<1 min
Duration	10 min	90–100 min	35–45 min	45–60 min	25–35 min	26–40 min
Continuous Infusion dose	N/A	1–2 μg/kg/min	0.8–1.2 μg/kg/min	1–10 μg/kg/min	2–12 μg/kg/min	10–12 μg/kg/min
Recovery	10–20 min	120–180 min	45–60 min	90 min	40–60 min	30-60 min
Renal failure	No change	Increased effect	Increased effect	No change	No change	
Hepatic failure	Increased effect (decrease dose)	Mild increased effect	Variable	Minimal to no change	Minimal to no change	30% increased effect
Active metabolites	Yes	Yes	Yes	No	No	Yes
Adverse effects	Apnea, bradyarrhythmia, cardiac arrest, cardiac dysrhythmia, hyperkalemia, hypersensitivity reaction, malignant hyperthermia, prolonged neuromuscular block, respiratory depression, rhabdomyolysis tachyarrhythmia	Apnea, bronchospasm, hypertension, prolonged neuromuscular block, respiratory failure tachyarrhythmia	Anaphylaxis, apnea, bronchospasm, hypotension, muscle weakness, prolonged neuromuscular block, tachyarrhythmia	Bradyarrhythmia, bronchospasm, hypotension	Anaphylaxis, bradyarrhythmia, bronchospasm, edema, erythema, hives, hypersensitivity reaction, hypotension, at larger than recommended doses, laryngeal spasm, muscle weakness, paralysis, tachyarrhythmia, at higher doses	Hypotension, hypertension, tachycardia, pruritus, nausea, wheezing, allergic reactions

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Table 22 Drugs for pediatric ICU delirium

Drug	Onset	Dosing	Adverse effects/Comments
Haloperidol (Haldol®))	3–20 min	IV: ***Age***: 0–1, or Bodyweight = 3.5–10 kg: Loading: 0.05 mg in 30 min Maintenance: 0.01–0.05 mg/kg/day, divided into 2–4 times daily ***Age***:1-3, or bodyweight = 10–15 kg: Loading: 0.15–0.25 mg in 30 min Maintenance: 0.05–0.5 mg/kg/24 h divided into 2–4 times daily Age: 3–18, or Body weight > 15 kg: Loading: 0.3–0.5 mg in 30 min Maintenance: 0.05–0.5 mg/kg/24 h divided into 2–4 times daily ***Age***: 16 years or older: 5 mg per day divided into 2–4 doses **Discontinue in patients with QTc > 500 ms**	• Monitor for electrocardiographic changes QT interval prolongation and arrhythmias • Extrapyramidal side effects • Neuroleptic malignant syndrome (rare) • Lowers seizure threshold • Causes sedation
Risperidone (Risperal®)	30–60 min	Drug form: 0.25, 0.5, 1, 2, 3, and 4 mg standard oral tablets **Patients 15–20 kg**: daily dose is 0.25 mg/day orally **Patients > 20 kg**: 0.1–0.2 mg oral; Maintenance: 0.2–2.0 mg/24 h	• **Has ORAL form only** • Extrapyramidal side effects • Risk of seizure • Sedation, drowsiness • Weight gain and increased appetite • Feeling hot or cold • Headache, dizziness • Restlessness feeling; sleep abnormalities • GI problems
Olanzapine[a] **(Off-label use)**	≤60 min	2.5–5 mg PO QHS 5–10 mg IM	• Monitor for electrocardiographic changes QT interval prolongation and arrhythmias • Extrapyramidal side effects • Lowers seizure threshold • Hyperglycemia • Peripheral edema • Causes sedation
Quetiapine[a] **(Seroquel) (Off-label use)**	No data	Median daily dose: 1–1.5 mg/kg/day Duration of treatment: up to 12 days	• Quetiapine produces less Parkinson-like effects than ziprasidone, risperidone, and olanzapine • Monitor for electrocardiographic changes QT interval prolongation and arrhythmias • Extrapyramidal side effects • Neuroleptic malignant syndrome (rare) • Lowers seizure threshold • Neutropenia • Hyperglycemia • Causes sedation

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There is limited trial data establishing safety, efficacy, or appropriate dosing of atypical antipsychotics

[a]Olanzapine and Quetiapine are not among the commonly used drugs for postoperative delirium and should be used cautiously if needed at all

Table 23 Stress ulcer prevention and treatment drugs

Agent	Dosing	Adverse effects/Comments
H2 blockers		
Ranitidine	Children 1 month to 16 years of age: 2–4 mg/kg twice daily	Headache, dizziness, mental status changes, thrombocytopenia
Famotidine	Oral 0.5 mg/kg once daily at bedtime or in 2 divided doses daily (maximum 40 mg daily); up to 1 mg/kg daily has been used	Dose adjustment needed for renal dysfunction Potential increased risk of nosocomial pneumonia Efficacy not stablished for stress ulcer prophylaxis
Proton pump inhibitors (PPI)		
Omeprazole	5 to <10 kg, 5 mg once daily 10 to <20 kg, 10 mg once daily ≥20 kg, 20 mg once daily	Respiratory effects, fever (in children 1–2 years of age), accidental injuries (in children 2–16 years of age)
Esomeprazole	Oral Children 1–11 years of age: 10 mg once daily for up to 8 weeks Adolescents 12–17 years of age: 20 or 40 mg once daily for up to 8 weeks IV Infants 1 month to <1 year of age: 0.5 mg/kg once daily	No adjustment needed for renal or liver dysfunction Potential increased risk of nosocomial pneumonia Potential increased risk of *Clostridium difficile* infection Many drug interactions IV administration ONLY for patients who cannot tolerate PO/NG administration
Lansoprazole	Children 1–11 years of age: ≤30 kg, 15 mg once daily >30 kg, 30 mg once Children 12–17 years of age: 15 mg daily	

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appropriate choice of these agents; no significant data is still available regarding the appropriate or the selected agent for pediatric critical care. Some of the selected agents are presented here in Table 23 (Reveiz et al. 2010; Giglia et al. 2016).

Anticoagulation and Thrombolysis Drugs

These drugs could be divided into four main subclasses (Ageno et al. 2012; Moffett et al. 2016):

- Anticoagulants (oral and parenteral forms).
- Antiplatelet agents.
- Thrombolytic agents.
- Novel oral anticoagulants.

Oral Anticoagulants

During recent years, the use of anticoagulants (especially oral anticoagulants) in pediatric cardiac surgery has increased, mainly in the following patient groups (Moffett et al. 2006; Jain and Vaidyanathan 2010; Donadini et al. 2012; Douketis et al. 2012; Salvin et al. 2016):

- Prophylaxis of thromboembolic events after Fontan surgery.
- Mechanical prosthetic valves which are much more increasingly used in pediatric patients.
- Kawasaki disease having large aneurysms.
- Primary pulmonary hypertension.
- Dilated cardiomyopathy patients who have severe left ventricular dysfunction.

For these indications, warfarin is the most commonly used drug; however, other agents (including dabigatran, rivaroxaban, and apixaban) are not yet available for pediatric labeling *but may be used in adult patients with congenital heart disease*. Their properties are presented in Tables 24, 25, and 26.

Table 24 Oral anticoagulant dosing, monitoring, and preoperative discontinuation

Anticoagulant	Half-life ($t_{1/2}$)/dose	Monitoring	Discontinue before surgery (days)/reversal agent	Mechanism of action
Warfarin (Coumadin®) http://packageinserts.bms.com/pi/pi_coumadin.pdf *Accessed April 9, 2016*	• 20–60 h • Individualized dosing • Initial bolus dosing of 0.2 mg/kg (maximum initial dose 10 mg) with adjustments on subsequent days based on daily INR • Alternative regime without bolus: age 2–12 years old: 0.09 mg/kg/day; age more than 12 years old: 0.08 mg/kg/day	• PT/INR	• Minimum of 5 days without reversal agents • Reversal agents. – **Vitamin K** 10 mg PO/IVPB for emergent *normalization* of PT/INR; IVPB initial effect at 2 h and full correction within 24 h 5 mg PO and 1 mg IVPB produce similar effects on INR at 24 h 0.5–1 mg orally for reducing PT/INR into *therapeutic range* (for <2.5 mg use IV form administered orally) Ineffective in hepatic disease due to inability to produce factors *Oral* route not effective in biliary disease SQ is not recommended due to unpredictable absorption and reversal characteristics – **Prothrombin Complex Concentrate** (PCC, Factor IX complex, Profilnine®) 25–50 units/kg *with* Vitamin K to prevent rebound increase in INR – **Recombinant activated factor VII** For intracranial hemorrhage—doses vary; 20–40 μg/kg have been used; available as 1-, 2-, 5- and 8 mg vial sizes; use the lowest dose rounded to nearest vial size and repeat if needed due to risk of arterial and venous thrombotic and thromboembolic events	Inhibits vitamin K epoxide reductase; in this way, warfarin prevents vitamin K1 regeneration after γ-carboxylation **PEDIATRIC LABELING is available**

(continued)

Table 24 (continued)

Anticoagulant	Half-life ($t_{1/2}$)/dose	Monitoring	Discontinue before surgery (days)/reversal agent	Mechanism of action
Dabigatran (Pradaxa®) https://www.pradaxa.com/ *Accessed April 9, 2016*	• 12–17 hours in healthy subjects • CrCl >30 mL/min: 150 mg BID. • CrCl 30-50 mL/min + dronedarone or ketoconazole: 75 mg BID • CrCl 15–30 mL/min: 75 mg BID	No readily available method • Activated Partial Thromboplastin Time (aPTT) demonstrates presence but not the degree of anticoagulation • Prothrombin time (PT) insensitive • Thrombin time (TT)-normal value rules out the presence of dabigatran • Ecarin clotting time (ECT)—linear dose relationship; not routinely available	• CrCl ≥50 mL/min: 1–2 days • CrCl 30–50 mL/min: 2–4 days • CrCl <30 mL/min: ≥5 days • Dialysis may remove up to 62% within 2 h • pINN: idarucizumab (dabigatran antidote) has been approved in 2015 by the FDA • (Glund et al. 2015; Pollack et al. 2015)	Dabigatran is among Direct thrombin inhibitors (DTI's) **PEDIATRIC LABELING not available yet**
Rivaroxaban (Xarelto®) http://www.xareltohcp.com/ *Accessed April 9, 2016*	• 5–9 h in healthy subjects • Atrial fibrillation • VTE prophylaxis • VTE treatment	No readily available method • Prolongs aPTT, PT/INR • No direct effect on platelet aggregation	• At least 1 day (24 h) • No reversal agent is available and unlikely to be dialyzable due to high protein binding	DirectfactorXa inhibitor (orally active) **PEDIATRIC LABELING not available yet**
Apixaban (Eliquis®) http://packageinserts.bms.com/pi/pi_eliquis.pdf *Accessed April 9, 2016*	• ~12 h following repeated dosing • Atrial Fibrillation	No readily available method • Prolongs aPTT, PT/INR • No direct effect on platelet aggregation	• 24–48 h before surgery depending on risk, location, and ability to control bleeding • No reversal agent and unlikely to be dialyzable due to high protein binding • Activated charcoal may be useful in overdose situations	DirectfactorXa inhibitor **PEDIATRIC LABELING not available yet**

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CrCl Clearance of Creatinine, *VTE* venous

Table 25 Parenteral anticoagulant dosing and monitoring *in Adults*

Anticoagulant	Half-life ($t_{1/2}$)/dose	Monitoring	Discontinue before surgery (h)/reversal agent
Unfractionated Heparin (UFH)	• 60–90 min • VTE: 80 unit/kg bolus, then 18 units/kg/hour • ACS: 60 unit/kg bolus, then 12 units/kg/hr • Prophylaxis: 5000 units SQ BID or TID	• aPTT • Anti-Xa activity level (UFH levels) • Activated clotting time (ACT; intraoperatively)	• 4–6 h • Protamine 1 mg/100 units of heparin (max 50 mg at a rate not to exceed 5 min) – Dose adjust based on time since heparin held: >60 min: 0.5 mg/100 units; >2 h 0.25 mg/100 units
Low molecular weight heparin Dalteparin (Fragmin®) *www.pfizer.com/files/products/uspi_fragmin.pdf* *Accessed 18 July* Enoxaparin (Lovenox®) *http://products.sanofi.us/lovenox/lovenox.html#section-14.1* *Accessed 18 July*	• 4.5–7 h • **VTE Treatment:** **Dalteparin:** 200 units/kg SQ daily **Enoxaparin:** 1 mg/kg SQ BID or 1.5 mg/kg SQ daily • **VTE Prophylaxis.** **Dalteparin** 5000 units SQ daily **Enoxaparin** 30 mg SQ BID or 40 mg SQ daily • **ACS** **Dalteparin**120 units/kg SQ every 12 hours **Enoxaparin** 1 mg/kg SQ every 12 h	• Anti-Xa activity level (LMWH level) • Dalteparin treatment doses should not be used in patients with CrCl ≤30 mL/min. • Enoxaparin 1 mg/kg SQ daily may be considered in patients with chronic stable kidney disease and CrCl ≤30 mL/min who are not dialysis-dependent; anti-Xa and serum creatinine monitoring is highly recommended	• 24 h • Protamine – <8 h after the last dose: 1 mg /1 mg enoxaparin or per 100 units of dalteparin – 8–12 h after the last dose or if repeat is necessary: 0.5 mg/1 mg enoxaparin or per 100 units of dalteparin – >12 h after the last dose: administration of protamine may not be necessary • The anti-factor Xa activity is never completely reversed (typically 60% is reversed)
Direct thrombin inhibitors Argatroban® *http://us.gsk.com/products/assets/us_argatroban.pdf* *Accessed 31 July 2012* Bivalirudin (Angiomax®) *www.angiomax.com/Downloads/Angiomax_PI_2010_PN1601-12.pdf.* *Accessed 18 July 2012*	• **Argatroban** 50 min **Treatment of HIT:** 2 μg/kg/min initial dose; adjust for hepatic insufficiency and critically ill patients with multisystem organ failure • **Bivalirudin**25 min **CPB dosing in setting of HIT**: **On pump**:1 mg/kg bolus, 50 mg for pump then 2.5 mg/kg/hour; goal ACT >2.5× baseline **Off pump:** 0.75 mg/kg bolus, 1.75 mg/kg/h: goal ACT >300 s	• aPTT	• 2 h • No reversal agent – Case reports suggest that recombinant factor VIIa 90 μg/kg × 1 may reverse the anticoagulant effect (Schulman and Bijsterveld)
Factor Xa inhibitor Fondaparinux (Arixtra®) *http://us.gsk.com/products/assets/us_arixtra.pdf* *Accessed 31 July 2012*	• 17–21 h • VTE **Prophylaxis**: 2.5 mg SQ daily **Treatment:** <50 kg: 5 mg SQ daily 50–100kg: 7.5 mg SQ daily >100kg: 10 mg SQ daily	• Not routinely available. International standards for the anti-Xa activity for UFH/LMWH do not apply	• 48 h • No reversal agent – Case reports suggest that recombinant factor VIIa 90 μg/kg × 1 reverse the anticoagulant effect (Schulman and Bijsterveld)

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Table 26 Parenteral anticoagulant dosing and monitoring in *Children* (Moffett et al. 2006; Monagle et al. 2008, 2012)

Drug	Mechanism of action	Dose	Half-life	Monitor/reversal
Anticoagulants				
Unfractionated Heparin (UFH)	UFH acts as an anticoagulant protein by binding to antithrombin and potentiating its anticoagulant activity over 1000-fold, inactivating coagulant factors IIa (thrombin), Xa, XIa, and XIIa	Initial loading bolus (if indicated): 75 U/kg over 10 min followed by age ≤1-year-old: continuous rate 28 U/kg/h, age >1 year old: continuous rate 20 U/kg/h	1.5 ± 0.5 h	Monitor: activated partial thromboplastin time (aPTT) and the UFH anti-Xa level Reversal: Full reversal with protamine sulfate Approximately 1 mg of protamine will neutralize 100 U of UFH. Calculations based on the total amount of heparin received in the prior 2–2.5 h
Low molecular weight Heparin: Enoxaparin	Similar to UFH, LMWH exert an anticoagulant effect through binding antithrombin and potentiating the antithrombin anticoagulant activity, but compared with UFH, there is a reduced inhibitory activity against factor IIa (thrombin) relative to factor Xa	Initial enoxaparin dose. Less than 3 months old: 1.7 mg/kg SC every 12 h Three months–2 years old: 1.2 mg/kg SC every 12 h More than 2 years old: 1 mg/kg subcutaneously every 12 h Obese patients approximately 0.8 mg/kg SC every 12 h to the maximum dose of 170 mg	3–6 h	Monitor: routine, same as heparin Reversal. LMWH can be partially reversed (≈70%) with protamine LMWH is easier to use in pediatric patients because it does not require a dedicated line, and frequent monitoring is not needed
Fondaparinux	A synthetic analog of the antithrombin-binding pentasaccharide found in heparin and LMWH enhances affinity for antithrombin, has no inhibitory activity against factor IIa (thrombin), and only inactivates factor Xa	0.1 mg/kg subcutaneous daily	17 h	Reversal: no reversal agents available
Argatroban **Parental DTIs**	A univalent DTI reversibly inhibits thrombin's catalytic site	initial infusion rate: 0.25–1 μg/kg/min	39–51 min	Monitor: aPTTs every 2–4 h to aim for an aPTT
Bivalirudin **Parental DTIs**	Is a bivalent DTIs, binds the active catalytic site of thrombin, as well as the thrombin/fibrinogen binding site	Bloused at 0.125 mg/kg IV and then an infusion of 0.125 mg/kg/hour is initiated	25 min	1.5–2.5 × Normal Reversal: the definitive reversal therapy is renal replacement therapy

Antiplatelet Agents

These agents are used extensively in adult patients, especially in those with acute coronary syndrome, cerebral vascular events, and thromboembolic events; however, in pediatric patients, these agents are used mainly to suppress platelet aggregation with an increasing trend especially and mainly in the following patients (Finkelstein et al. 2005; Soman et al. 2006; Mertens et al. 2008; Monagle et al. 2008, 2012; Maltz et al. 2009; Gentilomo et al. 2011; Jennings et al. 2012; Mohanty and Vaidyanathan 2013; Moffett et al. 2016):

- Hypoplastic left heart syndrome.
- Pulmonary artery anomalies (the latter two are the most common in pediatric cardiac surgery patients).
- Systemic to pulmonary artery shunts.
- Kawasaki disease.
- Primary prophylaxis for thromboembolic events in Fontan surgery in children.
- Prevention of thrombosis in prosthetic heart valves.
- Intracardiac devices or stents (e.g., after transcatheter closure of the atrial septal defect, until endothelialization of blood exposed parts is complete).
- Dilated cardiomyopathy (these patients are predisposed to thromboembolic events due to low cardiac output, poor contractility, and concomitant atrial fibrillation).
- Childhood arterial ischemic stroke: which may be due to some etiologies like sickle cell disease, congenital heart disease, arterial dissection, prothrombotic conditions, preceding viral infections, or idiopathic.
- In patients with left ventricular assist device.
- For treatment of vasculitis.

The antiplatelet drugs could be divided into the following categories based on their mechanism of action:

- Salicylic acid family including aspirin and triflusal.
  Aspirin is an irreversible cyclooxygenase inhibitor (inhibition of COX-1 and COX-2 activity).
  Triflusal (Disgren®) is a salicylate different from aspirin, which blocks cyclooxygenase, preserves vascular prostacyclin, and blocks phosphodiesterase.
- Adenosine diphosphate (ADP) receptor inhibitors which block P2Y12 component of ADP receptor on platelet surface (including **clopidogrel** "Plavix®", Prasugrel "Effient®", **ticagrelor** "Brilinta®", and **ticlopidine** "Ticlid®").
- Phosphodiesterase inhibitors leading to increased plasma level of cellular cAMP, finally blocking platelet aggregation in response to ADP like **cilostazol** (Pletal®) which is a selective **phosphodiesterase 3** inhibitor; or **dipyridamole** "Persantine®" which is both a **phosphodiesterase 5** inhibitor and an adenosine deaminase inhibitor; dipyridamole leads to adenosine and cyclic AMP accumulation, finally inhibiting platelet aggregation(Gresele et al. 2011).
- Glycoprotein IIB/IIIA inhibitors which are for intravenous use only and include **abciximab** "ReoPro®", **eptifibatide** "Integrilin®", **tirofiban**" Aggrastat®".
- Protease-activated receptor-1 (PAR-1) antagonists, mainly **vorapaxar** "Zontivity®," which prevent thrombin generation through blockade of thrombin-responsive receptor in platelets and vascular cells; pediatric label is not available yet(Capodanno et al. 2012; Wang 2015).
- Thromboxane inhibitors which include thromboxane synthase inhibitors and thromboxane receptor antagonists like **terutroban.**

A detailed pharmacologic description of some selected antiplatelet agents is presented in Table 27 (Dixon et al. 2009; Capodanno et al. 2012; Mauri et al. 2014; Giglia et al. 2016) (Tables 28 and 29).

Table 27 Oral and intravenous antiplatelet agents

Antiplatelet agent	Mechanism of action	Dose	Duration of effect	Half-life	Discontinue before surgery /monitor/ reversal
Oral antiplatelet agents					
Aspirin	Cyclooxygenase inhibitor (irreversible inhibition of COX-1 and COX-2 activity) Inhibiting the formation of thromboxane (TXA2) Inhibiting platelet activation and aggregation)	1–5 mg/kg/day (maximum: 91 mg)	7 days (since the affected platelets should be replaced)	5–20 minutes	3–5 days is needed before surgery to discontinue the drug; of course, depends on the residual aspirin effect desired No routine monitor No reversal agent is available For reversal, platelets (4–20 U/kg) may be given to counteract the platelet aggregation inhibition from ASA
Clopidogrel (Plavix®) http://www.plavix.com/Index.aspx *Accessed April 9, 2016*	Irreversibly blocks P2Y12 component of ADP receptor on platelet surface; also, platelet aggregation is prevented	≤2 years old: initial dose is 0.2 mg/kg/dose, once daily ≥2 years old: initial dose is 1 mg/kg/day; titrate to response 1 to 6 mg/kg/day for periods between 1 month and 6 months	7 days (since the affected platelets should be replaced)	The *t*½ of the parent drug is around 6 h; however, *t*½ of the active thiol metabolite is about 30 min	5–7 days No routine monitor No reversal agent available, Platelets 4–20 U/kg
Prasugrel (Effient®) http://www.effient.com/Pages/index.aspx *Accessed April 9, 2016*	Irreversibly blocks P2Y12 component of ADP receptor on the platelet surface		7 days (since the affected platelets should be replaced)		7 days
Ticagrelor (Brilinta®) http://www.brilinta.com/ *Accessed April 9, 2016*	Reversibly blocks P2Y12 component of ADP receptor on the platelet surface		48 h ($t_{1/2}$ 6–13 h including active metabolite)		3–5 days

Intravenous antiplatelet agents					
Abciximab (Reopro®) http://www.reopro.com/Pages/index.aspx *Accessed August 8, 2012*	Irreversible glycoprotein IIb/IIIa inhibitor		24 h		24 h
Eptifibatide (Integrilin®) http://www.integrilin.com/integrilin/index.html *Accessed August 8, 2012*	Reversible glycoprotein IIb/IIIa inhibitor	180 μg/kg bolus followed by infusion of 2 μg/kg/min If clearance of creatinine is <50 mL/min, 180 μg/kg bolus followed by infusion of 1 μg/kg/min	4 h		4 h
Tirofiban (Aggrastat®) http://www.aggrastat.com/ *Accessed August 8, 2012*	Reversible glycoprotein IIb/IIIa inhibitor	0.4 μg/kg/min × 30 min, then 0.1 μg/kg/min If clearance of creatinine is <30 mL/min, reduce dose by 50%	4 h		4 h
Dipyridamole; both IV and oral (Persantine®)	Inhibition of the activity of adenosine deaminase Another mechanism is to inhibit phosphodiesterase activity so the plasma level of cellular cAMP increases leading to blockade of platelet aggregation in response to ADP	1–5 mg/kg/day	40 min	10–12 h	No routine monitoring No reversal agent available, Platelets 10–20 U/kg

Table 28 Thrombolytic agents

Thrombolytic agent	Mechanism of action	Dose	Half-life	Discontinue before surgery / monitor/reversal
Thrombolytic therapy				
Alteplase (TPA) Recteplase Tenecteplase Urokinase Streptokinase	These are recombinant DNA-based products; biosynthetic forms of the enzyme *human tissue-type plasminogen activator* (tPA)	**Urokinase** Loading: 4400u/kg, Maintenance: 4400 μ/kg/h for 6–12 h **Streptokinase** Loading: 2000 μ/kg Maintenance: 2000 μ/kg/h for 6–12 h **tPA** 0.1–0.6 mg/kg/h for 6 h	5–10 min	Monitor: fibrinogen, TCT, PT, aPTT No reversal agent available

Table 29 Blood-related products (Groom et al. 1996; Durandy 2010, 2015; Payani et al. 2015, 2016; Sturmer et al. 2018; Dorgalaleh et al. 2019; Closson et al. 2020; Dennhardt et al. 2020)

Agent	Indication	Dose
Red packed cells	Perioperative bleeding	Estimated blood volume × (ideal hematocrit − actual hematocrit)/ Hematocrit 1 unit packed red blood cells
Platelets	*Qualitative or quantitative* platelet deficiency *Acute bleeding* and platelets below 50,000 mm^3 *Invasive procedures* and platelets under 50,000 mm^3 *Central nervous system* procedures and platelets under 100,000 mm^3	1–2 units/10 kg or 10–15 cc/kg
Fresh frozen plasma	Coagulation factors deficiency (liver disease, vitamin K deficiency, malabsorption syndrome, atresia of the extrahepatic biliary tract). – Disseminated intravascular coagulation – Emergency reversal of warfarin – Dilutional coagulopathy in massive transfusion – Replacement of specific coagulation factors (factors II, V, X, XI, XIII) – Hereditary angioedema – Microvascular bleeding with PT and extended TPT	Unit/10 kg or 10–15 cc/kg
Cryoprecipitate: Contains factor VIII (80 Units) Von Willebrand factor, factor XIII, fibrinogen (150–250 mg), and fibronectin	When *the concentration* of fibrinogen is less than 150 mg/dL and microvascular bleeding *Massive* transfusion with fibrinogen concentration under 150 mg/dL and active bleeding *Deficiency* of fibrinogen, dysfibrinogenemia, and afibrinogenemia	1 unit/5–10 kg

Table 29 (continued)

Agent	Indication	Dose
Desmopressin	*Congenital disorders*: von Willebrand disease: type I, contraindicated in type 2B; ineffective in type III Mild hemophilia: Effective for minoring procedures or dental extractions *Platelet function congenital disorders*: Bernard Soulier Syndrome *Vascular disorders*: Ehlher–Danlos, Marfan Syndrome Acquired disorders: Acquired Von Willebrand syndrome	Dose 0.3 μg/kg through an intravenous line
Fibrinogen concentrate	Hemorrhagic diathesis in congenital disorders such as hypofibrinogenemia, dysfibrinogenemia, and afibrinogenemia; acquired hypofibrinogenemias such as synthesis disorders, increased intravascular consumption, and hyperfibrinolysis	30–50 mg/kg
Prothrombin complex	Reverse Warfarin and for the treatment of bleeding in hemophilic patients with inhibitors and deficiency of specific coagulation factors; perioperative bleeding refractive to the use of fresh frozen plasma, platelets, and cryoprecipitate	20–30 UI/kg calculated with factor II
Activated recombinant Factor 7	Perioperative intractable bleeding when other measures have failed to control hemostasis	Dose: 40–80 μg/kg (Off-label dose in cardiac patients)
Concentrates of coagulation factors (like PCC, FEIBA)	Selective replacement of coagulation factors in uncontrollable postoperative bleeding leading to more direct and rapid correction of factor deficiencies	***PCC*** (Human Prothrombin Complex): which has factor IX with varying doses of other coagulation factors II, VII, and X ***FEIBA***: Factor eight inhibitor bypass activity

Antifibrinolytic Agents

Currently, there are two main available antifibrinolytic agents:

- Tranexamic acid.
- ε-Aminocaproic acid (EACA).

Both are recommended for perioperative use in pediatric and adult cardiac patients to reduce perioperative bleeding. Their mechanism of action is primarily a competitive binding to the lysine-binding location of plasminogen; the final result will be competitive prevention of plasma attachment to fibrin, and so, the process of fibrin degradation (called fibrinolysis) will be prevented. A detailed discussion on these agents is presented in chapter "Postoperative Bleeding and Coagulation Management". Also, a brief review is presented in Table 30 (Eaton 2008; Schouten et al. 2009; Faraoni and Goobie 2014).

Table 30 Dosing antifibrinolytic agents

Agent	Indication	Dose regimen
Epsilon-aminocaproic acid (Amicar®)	Perioperative bleeding in major pediatric cardiac surgery	100 mg/kg of body weight or 3 g/m^2 of body surface area during the first hour, followed by 33.3 mg/h or 1 g/m^2/h The total dose should not exceed 18 g/m^2/day No dose-ranging study is available
Tranexamic acid (Cyclokapron®)	Perioperative bleeding in major pediatric cardiac surgery	20–30 mg/kg loading dose IV, then 10–15 mg/kg/h infusion

Modified from Martin-Stone, S. "Postoperative Bleeding Disorders after Cardiac Surgery"; in "Postoperative Critical Care for Cardiac Surgical Patients". Dabbagh A., Esmailian F., Aranki S. F. Springer 2014, pp. 161-196. Published with kind permission of © Springer, 2014. All Rights Reserved

Antibiotic Prophylaxis in the Perioperative Period

The primary goal in antibiotic prophylaxis is to prevent surgical site infection using reliable, safe, cost-effective, and appropriate spectrum antimicrobial agent(s) which could cover all common pathogens during the perioperative period. There should be an assurance that the plasma and tissue level of such an antibiotic has reached the necessary level before starting the operation.

Cardiothoracic surgeries are often considered clean surgeries and in nearly all patients, the risk of superimposed perioperative infection is low. On the other hand, organ infection or deep surgical infections surgical site infection (SSI) in cardiac surgery patients (e.g., mediastinitis or prosthetic valve endocarditic), though not so much frequent, constitute a major condition that may at times lead to catastrophic outcomes with very high morbidity and mortality rate. However, if we include superficial SSI, greater percentages of patients are involved with postoperative SSI.

In pediatric cardiac surgical patients, there are some risk factors for SSI. Though risk factors for superficial SSI are not the same as risk factors for deep SSI (e.g., mediastinitis), a brief list of all these risk factors are presented here (Mehta et al. 2000; Allpress et al. 2004; Nateghian et al. 2004; Lepelletier et al. 2005; Iarussi et al. 2008; Costello et al. 2010; Bucher et al. 2011; Vijarnsorn et al. 2012):

- Younger patients (lower age).
- Longer surgical procedures (i.e., duration of surgery).
- More units of postoperative blood transfusions.
- Infancy (age <1 month).
- Underlying failure to thrive.
- Higher classes of ASA (American Society of Anesthesiologist score).
- Prolonged preoperative stay.
- Prolonged ICU stay (>3 days).
- Prolonged intubation.
- Prolonged inotropic support in ICU.
- Prolonged mechanical ventilation (>2 days).
- Prolonged hospital length of stay (>14 days).
- Prolonged postoperative hospital stay.
- Reopen procedures.
- Extubation failure (especially when a repeated failure occurs).
- Increased leukocyte band cell counts during the preoperative period and on the first postoperative day.
- Elevated serum lactate levels in the first postoperative day.

In Tables 31 and 32, a brief description of the commonly used antibiotic prophylaxis regimens is presented.

Table 31 Antibiotic prophylaxis for pediatric cardiac surgeries

Procedure	Common pathogens	Recommended antibiotic prophylaxis	Postoperative duration of antibiotic treatment
Congenital cardiac procedures (including but not limited to patent ductus arteriosis, atrial/ventricular septal defects, Glenn shunt, valve repair/replacement, prosthetic graft insertion, aortic reconstruction)	• *Staph epidermidis* • *Staph aureus* • *Coagulase-negative Staphylococcus* • *Escherichia coli* • *Pseudomonas aeruginosa* • *Haemophilus influenza nontype b*	**Cefazolin** OR **vancomycin** for known MRSA or high risk for MRSA, or major reaction to beta-lactams	Discontinue within 48–72 h of surgical end time
Ventricular assist devices (VAD)	*Staph epidermidis, Staph aureus, Streptococcus, Corynebacteria,* enteric-gram-negative bacilli *Candida*	Vancomycin 15 mg/kg IV within 60 min before surgical incision and q 12 h × 48 h Piperacillin-tazobactam 3.375 g IV within 60 min before surgical incision and q 6 h × 48 h Fluconazole 400 mg IV within 60 min before surgical incision and q 24 h × 48 h Mupirocin (Bactroban®) 2% nasal ointment applied to nares the night before, and morning of surgery (if nasal culture is positive for *S. aureus*)	Gram-negative coverage tailored to patient flora and/or institutional susceptibility × 48 h Mupirocin (Bactroban®) 2% nasal ointment to nares BID for 5 days (if nasal culture is positive for *S. aureus*)

Staph epidermidis, Staph aureus, Streptococcus, Corynebacteria, enteric-Gram-negative bacilli

Table 32 Commonly used antibiotics for prophylaxis in cardiac surgical patients

Antibiotic agent	Intra-operative redosing with normal renal function	Timing of the first dose	Time for effect	Redosing time (minutes)
Cefazolin	25 mg/kg q 6–8 h (max 1000 mg; if greater than 80 kg, use 2000 mg)	Begin 60 min or less before incision	30	Every 6–8 h
Cefotaxime	20–30 mg/kg	Begin 60 min or less before incision	30	Every 6 h
Cefuroxime	50 mg/kg	Within 1 h prior to incision	15–60	Every 4 h
Clindamycin	5–10 mg/kg up to 900 mg	Begin 60 min or less before incision	30	Every 6–8 h
Vancomycin	10 mg/kg (up to 1000 mg if >50 kg)	Begin 60 to 120 min before incision	60	Every 6 h

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Perioperative Care of the Congenital Cardiac Patient in the Cardiac Catheterization Laboratory

Lorraine N. Lubin and Robert Wong

Abstract

New innovative techniques in cardiac catheterization (cath) procedures and advances in technology in the field have created an environment in which the primary objective has advanced from diagnostics to a minimally invasive therapeutic intervention. These advances and new devices have provided nonsurgical alternatives for the treatment of congenital heart disease, which in many instances have replaced open cardiac surgery and decreased the morbidity and mortality for multiple goals of therapy. While the ultimate outcome for the patient is a more minimally invasive therapy, the catheterization lab has taken on more of an operating room setting requiring more intensive monitoring and higher-acuity anesthetic management. With the survival of congenital heart patients increasing and creating a situation in which there are more adults with congenital heart disease than pediatric patients, the patient population of the pediatric cath lab reflects the demographics of the specialty. The pediatric cath lab is now more correctly referred to as the congenital cardiac cath lab with the capability of caring for all patients, irrelevant of age by a single group of providers.

Keywords

Congenital heart disease · Pulmonary vascular resistance · Hypoplastic left heart syndrome · Hybrid procedure · Brachial plexus injury

Introduction

New innovative techniques in cardiac catheterization (cath) procedures and advances in technology in the field have created an environment in which the primary objective has advanced from diagnostics to a minimally invasive therapeutic intervention. These advances and new devices have provided nonsurgical alternatives for the treatment of congenital heart disease, which in many instances have replaced open cardiac surgery and decreased the morbidity and mortality for multiple goals of therapy. While the ultimate outcome for the patient is a more minimally invasive ther-

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apy, the catheterization lab has taken on more of an operating room setting requiring more intensive monitoring and higher-acuity anesthetic management. With the survival of congenital heart patients increasing and creating a situation in which there are more adults with congenital heart disease than pediatric patients, the patient population of the pediatric cath lab reflects the demographics of the specialty. The pediatric cath lab is now more correctly referred to as the congenital cardiac cath lab with the capability of caring for all patients, irrelevant of age by a single group of providers White (2011).

In the past years, anesthesia providers were not significantly involved in the care of patients in the congenital cath lab, and cardiologists were responsible for prescribing the sedation medications used during the procedure. However, as the acuity of the interventions has increased and hybrid operating rooms have emerged, the cath lab has morphed into a near-operating room setting in which anesthesia machines, medication carts, and airway equipment have come to essentially every room. With respect to the perioperative risks in the cardiac cath lab, the data from the Pediatric Perioperative Cardiac Arrest Registry has shown that approximately one-third of cardiac arrests occur in children with congenital heart disease (CHD), of which 17% occur during cardiac cath procedures. With this in mind, the anesthesiologist must not only be familiar with the patient's congenital physiology, but it is also critical for the appropriate monitoring equipment, blood availability, surgical backup and postoperative disposition to be arranged.

The Cath Lab Environment

The environment of the cath lab differs from the operating room environment in important ways with respect to the anesthesia and surgical setting. The procedures include both adults and children with varying levels of acuity which range from outpatient procedures to the hybrid cases and care of patients on significant forms of medical and device support. The staff in the cath lab is generally not trained in open surgical procedures and is very focused with respect to their scope of practice. More and more anesthesia providers are becoming the mainstay of the cath lab as the procedures become more invasive such as valve implantation, surgical pacemaker implantation, complex percutaneous coronary interventions (PCI), ventricular assist device placement, aortic interventions, and hybrid procedures. Hybrid procedures involve varying levels of open surgical intervention and catheter-based intervention and also rely on multiple imaging techniques such as echocardiography and fluoroscopy. One of the many challenges of the cath lab apart from the evolving new technology and roles of various specialties is the workspace. Due to the fluoroscopy equipment, the space for anesthesia providers is limited, and special equipment and support personnel are not readily available. This makes emergent resuscitation more difficult. In modern-day facilities, the cath lab is designed to be adjacent to or relatively near the cardiac operating rooms. The advent of hybrid suites which are larger than the average cath lab suite is also being developed. Hybrid suites encompass equipment needed for both catheter-based interventions and open cardiac surgical procedures. Hybrid suites contain supporting equipment for perfusionists such as the cardiopulmonary bypass (CPB) machine and extracorporeal membrane oxygenation (ECMO). Since a hybrid room is designed for open cardiac procedures, the room must meet the standards of an operating room-anesthetizing location with appropriate air exchange, gases, electrical outlets, gas scavenging, suction and room for the CPB machine, and anesthesia machine, and medication/supply cart as well as important equipment such as echocardiography machines.

MRI scanners are also becoming a more important imaging modality and are replacing cardiac cath in some diagnostic situations. If MRI is part of the cath plan, the patients are frequently moved under the same anesthetic and monitoring equipment, and timing is crucial. The patient must be kept in an MRI-compatible gurney, and monitoring equipment as well as infusion pumps must also be MRI compatible.

Radiation safety is another important consideration in the cath lab environment. Cardiac cathe-

terization which uses cine fluoroscopy can deliver relatively high doses of radiation. There is no known safe exposure for either patients or providers, which are accepted to decrease cancer risk. It is recommended to wear dosimeter badges and follow the radiation safety principles advised to reduce the occupational exposure: (1) Wear proper radiation lead clothing shields and protective lead eyewear. (2) Minimize exposure time. (3) Maintain the maximal distance acceptable to the source of the radiation, and use lead screens whenever possible. With respect to the risk to the patient, there is an increased risk with increasing dose, and the average dose used during both diagnostic and therapeutic cases remains relatively high with the youngest patients frequently receiving the highest exposures. In 2006, a study was released which looked at the chromosomal damage in patients with CHD; there was a distinct correlation that cardiac cath was associated with long-term chromosomal damage Andreassi (2009).

The Goals of Congenital Cardiac Catheterization

Diagnostic catheterization for patients with CHD is important to further delineate the patient's anatomy, physiology or hemodynamics, biventricular function, and responsiveness to medications as well as respiratory interventions. The information obtained from catheterization data is vital in many cases for appropriate surgical decision-making in a relatively fragile patient population. The circumstances in which the cath data is obtained are extremely important due to its effects on the calculated hemodynamic data. For example, hemodynamic data is acquired on room air settings, and dissolved oxygen is minimized or accounted for in the calculated data. The effects of positive-pressure ventilation, sedation, or other inotropic or vasoactive medications must also be factored in when accessing the final data and imaging. The communication between the anesthesiologist and interventional cardiologist is vital in the management of these patients.

Diagnostic cath is only one of multiple imaging modalities used to correctly access the congenital heart patient's anatomy and physiology and in many cases is not necessary for many patients requiring surgery. Advances in other imaging techniques most notably echocardiography, and MRI compared to the invasive nature of cardiac cath and its associated complications such as vascular compromise, require that significant consideration must be given to the indications for diagnostic catheterization.

In 2011, the American Heart Association put forth its recommended indications for diagnostic congenital cardiac catheterization which comprise the following indications:

1. To perform the measurement of central and peripheral intravascular pressures and derive hemodynamic information including pulmonary vascular resistance (PVR), systemic vascular resistance (SVR), shunt fractions, oxygen consumption, and cardiac output.
2. To define cardiac and vascular anatomy: Cardiac catheterization in conjunction with echocardiography and MRI may be needed in patients with complex anatomy and in previously operated patients in whom the anatomy is not known from operative reports.
3. To evaluate the myocardial function and assess the effects of respiratory interventions and medications on the cardiovascular system: These types of diagnostic catheterizations are frequently performed on patients who have single-ventricle anatomy when deciding upon the timing of the procedure or its appropriateness. It is also common for patients with pulmonary hypertension or as part of a transplantation evaluation to undergo this type of diagnostic cath.
4. Coronary artery angiography, endocardial biopsies, and evaluation of myocardial function are parts of the routine surveillance of patients following cardiac transplantation. Endocardial biopsy is also indicated in the face of acute cardiac decompensation from possible viral myocarditis or other forms of myocarditis or cardiomyopathy.
5. To obtain a diagnostic evaluation as part of an interventional procedure.

Procedural Vascular Access and the Approach

The routine approach for vascular access and diagnostic cath in patients with biventricular hearts is to cannulate the femoral vein and artery using the Seldinger technique. For patients with univentricular hearts, access is frequently obtained by the internal jugular or subclavian vein in order to evaluate the pulmonary arteries subsequent to cavopulmonary connections or Glenn procedures. After placement of appropriate-sized sheaths, the catheters are advanced through the vascular and heart chambers where pressures and oxygen saturation measurements are made in the appropriate sequence. The oxygen saturation measurements of the cardiac chambers and vasculature will facilitate the detection of shunts and allow the calculation of shunt fractions, oxygen consumption, cardiac output, and pulmonary blood flow. The oxygen saturation data is obtained on room air to avoid error in the calculations, and the angiograms are generally performed after the physiologic measurements have been made.

In patients with CHD, vascular access can be extremely challenging. Vascular thrombosis and injury are common sources of morbidity in this population which includes neonates and the adult congenital patients. With the advancement of interventional procedures including occluder devices and transcatheter valves, much larger vascular sheaths are required to deploy these devices and increase the risk of vascular injury.

Anesthetic Considerations in Diagnostic and Interventional Cardiac Cath Procedures

Procedures both diagnostic and interventional in the cath lab differ from open surgical cases in a number of important ways. Cath procedures in general are not associated with major fluid shifts, significant systemic inflammatory responses, or severe postoperative pain. The most stimulating portion of the procedure with respect to pain occurs during the attaining of vascular access, and in many cases, the procedure can be performed as a same-day procedure. However, unlike patients who generally have outpatient surgery, the patients presenting to the congenital cath lab frequently have severe underlying cardiac disease and other significant comorbidities. The underlying illness as well as the proposed procedure with significant frequency can result in severe, life-threatening events, which require the expertise of a congenital cardiac anesthesiologist working with the interventional cardiologist to ensure perioperative hemodynamic stability.

In the past years, a topic of controversy has been which provider is responsible for the administration of sedation and monitoring for patients undergoing congenital cardiac catheterization. Prior to anesthesia providers being responsible for the management of patients in the cath lab, the respective cardiologist was in charge of ordering nurse-administered sedation with variable levels of success and morbidity. While this practice may be adequate for an adult patient who may be cooperative during a limited diagnostic catheterization, congenital heart patients require a different approach. The challenge of vascular access, younger patients who are unable to cooperate, patients with severe life-threatening comorbidities, and the risk of severe hemodynamic instabilities, has created a medical scenario in which anesthesiologists are considered essential members of the congenital cath lab team. In recent years, the American Society of Anesthesiologists published guidelines which state that any provider of sedation must be able to rescue the patient if the level of sedation is deeper than intended. It is also required that any provider of sedative medications has knowledge of the pharmacology of the medications used and any potential interactions with the underlying disease and multi-organ system dysfunction as well as the ability to manage the airway on a wide variety of patients, which may have coexisting syndromes that affect the airway anatomy. With this in mind, anesthesia providers considered the standard of care for congenital heart patients undergoing cardiac catheterization. These patients irrespective of the anesthesia technique chosen require

the same perioperative assessment and intraprocedure monitoring, which are comparable to that of an operative case.

In the United Kingdom, all children undergoing cardiac catheterization receive a general anesthetic for the procedure. In the United States, the technique employed is based on the needs of the procedure and the underlying illness of the patient. There are instances where conscious sedation may be appropriate for a diagnostic procedure where the patient can cooperate, and the data required may be more optimal in the case of a spontaneous breathing patient. However, endotracheal intubation is recommended for most interventional cath procedures especially when the patient may be at risk for ventilatory failure due to illness, underlying disease state, and prematurity, risk of hemoptysis; risk of significant hemodynamic disturbances exists; the need for suspension of respirations such as in 3D reconstruction imaging; the need for TEE; and the risk of patient movement or coughing during a critical point in the procedure.

Premedication for diagnostic or interventional catheterization procedures is recommended for patients who require medication for procedural anxiety. Midazolam 0.5–0.75 mg/kg orally is considered safe and effective and generally has a rapid onset. For adult congenital patients who require pre-procedural premedication, midazolam given by slow IV titration is recommended. These patients may be very medically fragile with multiorgan system dysfunction and require vigilance with respect to sedation medication and their hemodynamic response.

Preoperative Assessment

The preoperative assessment for the patient undergoing cardiac cath should be as comprehensive as that for any operative procedure with focus on the cardiovascular system. Any signs and symptoms of worsening heart failure or cyanosis should be elicited such as shortness of breath, diaphoresis, tachypnea, fatigue, poor feeding or feeding intolerance, and a decrease in baseline saturations. It is even more crucial in the patient with CHD to review any perioperative respiratory illnesses as this can lead to severe perioperative respiratory compromise and an increase in PVR above baseline. If a history of perioperative respiratory infection is elicited, the case should be rescheduled for an appropriate future date. The airway assessment is extremely important as the risk of concomitant syndromes in patients with CHD remains significant. Airway equipment should be appropriately sized and available in the cath lab prior to induction. If the patient is undergoing a mask induction and IV access is to be obtained after general anesthesia is induced, it is advised that ultrasound and other equipment useful in obtaining IV access are readily available. Difficult IV access is a recognized problem in this patient population, and a review of previous operative reports or cath reports is recommended to help delineate what access sites are potentially available.

Intraoperative Management

The type of anesthetic and the induction technique employed are dependent on the nature of the procedure planned and the baseline functional state of the patient. Inhalational induction with sevoflurane is generally well tolerated when titrated to effect and IV access is obtained in an expeditious fashion. There are patients who are considered extremely medically fragile, and preinduction IV access is considered the safest plan. This can frequently be achieved with mild oral sedation with midazolam and ketamine or other non-IV regimens and topical EMLA cream. If a hybrid procedure is planned or there is a need for perioperative invasive monitoring, an arterial line and CVP can be placed with avoidance of the site required for the procedure. Positioning also needs to be considered for the CHD patient undergoing cath in that the arms are usually placed above the head to optimize the cardiac biplane imaging and 3D reconstructions. Vigilance is needed to avoid brachial plexus injury in this scenario, and the arms must be checked frequently and intermittently relaxed and repositioned.

The hemodynamic changes which accompany the induction and maintenance of anesthesia need to be appreciated when interpreting the data acquired from a diagnostic cath and in ensuring hemodynamic stability for an interventional cath. While the anatomy of a given patient will not be altered by anesthetic manipulations and medication, the physiology of a patient is affected in a dose-dependent and generally predictable manner. The measurements obtained must be interpreted in the context in which they were obtained with appreciation given to the hemodynamic effects of the respective anesthetics used as well as any vasoactive medications and the manner of ventilation employed. Careful selection of the agents used and appropriate titration will help minimize untoward hemodynamic effects. The most common hemodynamic effects of anesthetic medications during a congenital heart cath are depression of the systemic blood pressure, changes in arterial saturation and carbon dioxide concentration, decreases in SVR, and changes in PVR, cardiac output, oxygen consumption, and shunt flow. Maintaining systemic blood pressure under anesthesia can be a challenge as most anesthetic agents cause a direct reduction in SVR, and a reduction in cardiac output can also result from the negative inotropic and chronotropic effects of these agents and from decrease preload secondary to vasodilation and positive-pressure ventilation. The hemodynamic effects of anesthetics tend to be more significant in sicker patients with less ability to compensate. Careful dosing of all agents is recommended as well as judicious fluid management. If vasopressors are required, the use should be communicated with the cardiologist as they will influence the obtained data. In addition, cardiac output will decrease under general anesthesia secondary to a reduction in whole-body oxygen consumption.

Another important consideration is the manner in which a patient is ventilated. A recent study reported a transition from positive-pressure ventilation to negative-pressure ventilation or spontaneous breathing, increasing the cardiac output by 11% in otherwise healthy children, 28% in post-operative cardiac patients, and 54% in patients with Fontan physiology. High oxygen concentrations in patients with large left-to-right shunts can significantly lower the PVR, therefore increasing the left-to-right shunt with a significant increase in the Qp:Qs ratio. Additionally, changes in arterial carbon dioxide concentrations or pH will significantly affect pulmonary blood flow. Also, small changes in pulmonary vein oxygen saturations will create large changes in the calculation of the shunt fraction. The advantages and disadvantages of positive- versus negative-pressure ventilation are numerous and relatively predictable. With respect to acquiring the most accurate cath data and optimizing cardiac output, a patient would be spontaneously breathing, on room air with an unobstructed airway and an intact respiratory drive. However, this is rarely possible in an operative or procedural situation, and the best decision is generally one in which the patient has an unobstructed airway or protected airway with controlled ventilation which prevents hypercapnia and atelectasis. Consistency in the approach to the ventilation is important in the management of these patients, with respect to the interpretation of the data among the treatment team.

Anesthetic Agents Used in Congenital Cardiac Catheterization

Many different regimens of anesthetic agents have been used in congenital cardiac cath cases as a single agent or as a combination. At this time, there is no ideal agent that has been identified that can be used in all cases. The following is a discussion of a variety of agents and their known hemodynamic effects and advantages and disadvantages Abbas et al. (2012).

Volatile Anesthetic Agents

The volatile anesthetic agents have been used safely in congenital heart patients of all ages for many years despite the concerns of depressed contractility and decreased SVR. These agents are known to decrease blood pressure in a dose-dependent fashion and attenuate hypoxic pulmo-

nary vasoconstriction, thereby worsening V/Q mismatch. The most commonly used agents in the United States are isoflurane, which is thought to have the least myocardial depression and sevoflurane which also has a relatively safe hemodynamic profile. The advantage of sevoflurane is the ability to use it during a mask induction in conjunction with nitrous oxide and later as a maintenance agent. The actual MAC of the volatile agent may be just enough to ablate awareness and can be used in combination with narcotic medication, benzodiazepine, and muscle relaxant. Nitrous oxide is frequently used during the initial mask induction and then discontinued due to the potential for significant increases in PVR in adult patients with pulmonary hypertension. There has not been evidence to show the deleterious effects of nitrous oxide on the pulmonary hemodynamics in infants with or without pulmonary hypertension. Nitrous oxide is also used with caution in this patient population due to the risk of paradoxical emboli and the risk of worsening a venous air embolism, which can occur as a result of air introduced with central venous cannulation.

Propofol

Propofol has been used safely with efficacy in the congenital cardiac population during cath lab procedures and induction. Propofol has less emergence delirium and offers more rapid recovery. The antiemetic properties also help decrease the incidence of postoperative nausea and vomiting. There are dose-dependent decreases in SVR, blood pressure, heart rate, and contractility, which make it a less favorable agent in patients with fragile hemodynamics. It has no effect on PVR or pulmonary artery pressure (PAP). Caution must be exercised when considering the use in patients with aortic stenosis, systemic-to-pulmonary artery shunts, pulmonary hypertension, diminished ventricular function, and single-ventricle physiology. Propofol is an IV general anesthetic and causes respiratory depression and loss of airway reflexes which can lead to airway obstruction and hypercarbia in unintubated patients and result in hemodynamic compromise.

Opiate Medications

Opiate medications do not have amnestic properties and cannot be used as a single anesthetic agent alone but are efficacious analgesics, which are part of a balanced anesthetic. Opiates such as fentanyl have minimal hemodynamic effects and have been used safely for patients with CHD. They are recognized to be efficacious in attenuating the pulmonary vasoconstrictive response to noxious stimuli. Opiates are known to have associated bradycardia and significant respiratory depression, which cause hypoventilation and hypercarbia. Opiates such as morphine that causes significant histamine release can adversely affect the PVR. Remifentanil that is used as an infusion and titrated to effect has been used with hemodynamic stability but at higher doses has been noted to cause problems with electrophysiological cases due to slowing of the sinus node function and atrioventricular node function. Fentanyl is the most commonly used opiate in pediatric congenital cardiac surgery and is frequently used as an infusion and later after extubation is switched to a longer-acting opiate medication such as morphine or Dilaudid. Opiates are associated with postoperative nausea and vomiting and require antiemetic medications to be used in conjunction in many patients.

Benzodiazepines

Benzodiazepines are anxiolytic medications, which have been used with good efficacy in patients with CHD and in the setting of the cath lab are frequently used as a premedication. In general, the class has minimal hemodynamic and respiratory depression when appropriately titrated. In pediatric patients, oral midazolam is frequently used as a premedication, while in older patients it is given in the IV form. Midazolam is also used as an intraoperative sedative in cooperative patients and to prevent intraoperative awareness in the setting of cardiac surgery due to its amnestic properties. When used with volatile agents such as sevoflurane, midazolam can attenuate the emergence of delir-

ium, dysphoria, and hallucination caused by ketamine. When used in combination with opiate medications, there can be significant respiratory depression, and appropriate titration and monitoring are warranted.

Ketamine

Ketamine is used for both procedural sedation and is an important induction agent and premedication. Ketamine is unique in that it has profound analgesic properties as well as being a powerful sedative hypnotic that actually allows preservation of airway reflexes and ventilatory drive. The most important characteristic regarding ketamine is the preservation of stable hemodynamics. Isolated myocardium shows a negative inotropic effect; however, the sympathomimetic effects of ketamine offset the potential negative inotropic effect, which is not generally appreciated clinically. Ketamine does increase oxygen consumption, which can create a potential error in the hemodynamic calculations unless the oxygen consumption is directly measured. Ketamine is also unique in that PVR and PAP remain essentially unchanged in patients with pulmonary hypertension. The disadvantages of ketamine include increased salivation, nausea, dysphoria, prolonged wake-up, and myoclonus. The stable hemodynamics on induction make it a preferred agent with the side effects frequently offset with antiemetic medications such as ondansetron and anti-sialagogue effects of glycopyrrolate, which also prevents bradycardia associated with direct laryngoscopy. The potential dysphoria or hallucinations can be offset with midazolam or propofol, which is frequently used in conjunction with ketamine.

Dexmedetomidine

Dexmedetomidine is a potent, new medication that can be given by bolus and more frequently as an infusion. It is a sedative, centrally acting alpha-2 agonist, which causes sedation, anxiolysis, and mild analgesia with some moderate hemodynamic effects. Significant respiratory depression is generally avoided; however, there is considerable sinus node and atrioventricular node depression with resultant bradycardia in a dose-dependent manner Wong et al. (2012). Dexmedetomidine is generally not recommended for electrophysiological cases, and its bradycardic side effects are frequently utilized in instances of dysrhythmia such as junctional ectopic tachycardia and other forms of tachycardia. It is generally not recommended in patients at risk for heart block or bradycardia as well as patients who are rate dependent such as neonates and patients with single-ventricle physiology, impaired ventricular function, and significant regurgitant lesions Tobias et al. (2011).

Complications in the Congenital Cath Lab

The incidence of significant complications in the congenital cath lab is reported to be between 7 and 24% with complications being more frequent in the interventional procedures relative to the diagnostic cases. Mortality in the congenital cath lab remains reported at less than 1%. The most commonly reported complications are vascular injuries and dysrhythmias Ramamoorthy et al. (2010). Less commonly reported but significant complications include bleeding, stroke, vascular rupture, cardiac tamponade, valvular damage, vascular thrombosis, air embolus, retained foreign body/catheter, device embolus, contrast reaction or anaphylaxis, and brachial plexus injury. The most significant risk factors for major morbidity or complication in the cath lab include age of less than 1 year, smaller patient size, and complexity of intervention Mehta et al. (2008). Arrhythmias are common and generally transient. Risk factors for arrhythmias include hypercarbia, electrolyte disturbances, catheter manipulation, cardiac ischemia, drugs, coronary air embolus, and myocardial and conduction tissue damage. Pacing capability should be available as well as defibrillators and antiarrhythmic medications. Patients with severe pulmonary hypertension are also at significant risk for mortality in the cath lab. The risk of periprocedural

cardiac arrest is well documented in patients with CHD. The Pediatric Perioperative Cardiac Arrest Registry shows that approximately one-third of cardiac arrests occur in children with CHD of which 17% occur during cardiac cath procedures Odegard et al. (2014). The risk factors for procedural cardiac arrest in the cath lab include age of less than 1 year, single-ventricle physiology, and preoperative cath procedures. The risk of cardiac decompensation in the congenital cath lab requires that surgical backup is immediately available for potential rescue and rapid deployment of mechanical circulatory support Bergersen et al (2010).

Hybrid Procedures

Hybrid procedures incorporate both surgical and transcatheter techniques as part of a single operative procedure to treat CHD. Most frequently, hybrid procedures are employed to treat hypoplastic left heart syndrome (HLHS) in which a PDA stent is deployed and bilateral PA bands are placed with an open sternotomy. The use of CPB is deferred as well as aortic cross-clamping, which avoids the myocardial injury and inflammatory response associated with open heart procedures as well as possible neurologic injury. Hybrid procedures are also used to close VSDs, implant pulmonary valves, and branch PA stents as well as a number of other minimally invasive procedures. The anesthetic management of a hybrid procedure is dictated by the nature of the procedure. The hybrid suite is an operating room with full cath lab capabilities as well as cardiac operating room capabilities. The ability to attempt a catheter-based intervention with conversion to open surgery is another advantage of the hybrid suite.

Conclusion

The congenital cardiac cath lab has moved to a new era of therapeutic intervention with patients being intervened on at younger ages and with more invasive procedures with potential for significant hemodynamic instability. The anesthetic challenges of the congenital cath lab include the frequently remote location of the suite, sicker and younger patients, higher potential for respiratory and cardiac instability, as well as environmental issues such as significant radiation exposure. The importance of communication with the interventional cardiologist is a vital factor regarding patient status during a procedure, and the availability of surgical backup and mechanical circulatory support is essential considering the risk of cardiac instability. Multidisciplinary team collaboration as well as vigilance and preparation create the safest atmosphere to provide the patient with CHD a good procedural outcome.

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Perioperative Imaging for the Pediatric Congenital Cardiac Patient

Gary M. Satou and Mark S. Sklansky

Abstract

Perioperative imaging in congenital heart disease is a complex undertaking that requires a deep understanding of cardiac anatomy, cardiac pathology, clinical correlations of these components with the child, and advanced echocardiographic concepts. This chapter focuses specifically on these aspects of perioperative imaging as they relate to the operating room—intraoperative dynamics and the imaging details involved in optimally providing echocardiography and care to pediatric congenital cardiac patients undergoing cardiac surgery.

Keywords

Echocardiography · Transesophageal Epicardial · Preoperative imaging Intraoperative imaging · Congenital heart disease

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Introduction

Imaging in the operating room for congenital cardiac surgery is an important and fundamental component of optimizing outcomes and reducing morbidity and mortality in the current era. For decades, transesophageal and epicardial echocardiography has been used in this setting, and as an ultrasound machine and probe technology have advanced, it has allowed imagers to keep up the advances in complex surgeries and repairs. In fact, in the last few years, major guidelines have been published or updated that assist the imager with comprehensive information regarding image performance, acquisition, and key points to provide the surgical team Puchalski et al. (2019), Ayres et al. (2005). In this chapter, we will focus on intraoperative imaging for the pediatric congenital cardiac patient, including several case examples with decision-making, imaging details, as well as acknowledging some of the limitations that can be encountered.

Philosophic Approach and Intraoperative Decision Making in the Operating Room

Congenital cardiac imagers can be cardiologists or anesthesiologists (or even surgeons!), but what is most imperative is that the individual realizes he or she is part of a large, complex team

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made up of many people performing different roles. First and foremost, there is the surgical team, made up of several cardiac surgeons, nurses, and technical assistants. There is the perfusion team that is running the cardiopulmonary bypass circuit, and then there are the anesthesiology team members who are caring directly for all facets of the patient. The operating room is a dynamic and somewhat intense environment. Nonetheless, the imager needs to be able to obtain specific and detailed information in a short amount of time. As well, honesty and transparency are very important. If something is identified on preoperative imaging that deviates or is different from the prior information or anatomy, this must be conveyed to the team. As well, when performing the postoperative interrogation, at times the findings are somewhat disappointing or suboptimal with regard to the surgical goal at hand. In these cases, the imager must also be able to communicate and demonstrate in a truthful fashion what the residual lesion or lesions are, in order to provide the surgery team an opportunity to return to bypass and improve the repair Madriago et al. (2016). While this may sound straightforward, in the real world, executing such a delicate process may not be so easy. Sometimes there is a difference in opinion regarding a finding or a need to improve a repair, and it is important for all team members involved to be egoless and put the child's well-being first and foremost. Thus, the utmost of integrity from all team members should be manifest when undergoing such a thorough and important discussion/decision regarding the repair at hand. While the imager provides the echocardiographic information, many other variables play a role. The anesthesiology and surgical team members provide additional clinical data points. The patient's loading conditions and central venous pressure, along with the blood pressure, heart rate, rhythm, right ventricle, and pulmonary artery pressures, all may play an important role in the team's assessment of the child's repair at that moment. At times, a decision to return to bypass and attempt revision of a repair can be difficult—not only technically and medically, but also in an unspoken way, in that at times there may be a general sense of urgency in the room to move on with finishing a case, perhaps to start the next case or for other workflow reasons. While these factors cannot play a role in the decision, they may remain common themes of practical daily workflow in the operating rooms.

Another important factor in intraoperative decision-making is that which occurs before the operating room. It is imperative that every neonate or child heading to an operating room has undergone extensive echocardiography or advanced imaging with expert personnel so that there are no, or very few, questions regarding the cardiac anatomy at hand during the day of the surgery Hahn et al. (2022).

In the operating room, the preoperative assessment should simply be an interrogation of the heart and structures while under the unique loading conditions of the operating room and while under general anesthesia Randolph et al. (2002). This helps lay the groundwork for when the repair is completed, and interrogated, postoperative. The postoperative imaging can be compared to the findings at the beginning of the case, so a "before and after" type of comparison Rosenfeld et al. (1998). For example, reviewing the degree of residual aortic regurgitation after aortic valve repair is best compared to the preoperative imaging in the OR, not the last surface echocardiogram performed in clinic. Such a preoperative study may have been performed long ago, and likely while awake and with somewhat different loading conditions. The same can be said for evaluating myocardial function, valvular stenosis, and the myriad other types of congenital cardiac malformations that we routinely image and operate upon in the operating room. The key is to have an adequate set of preoperative images obtained in the operating room before the initia-

tion of the repair, in order to optimally interpret the immediate postoperative echocardiographic findings Nicoara et al. (2020).

Technology

Standard technology in the current era for pediatric congenital cardiac surgery imaging should include a state-of-the-art, full size ultrasound machine with the ability to scan 2D and 3D echocardiography and Doppler, with the standard pediatric probes that enable this, as well as pediatric and adult size multiplane TEE probes Salandin et al. (2010). Preferably, a micro-mini TEE probe is available for the small or preterm neonate or infant. In addition, a small, high-frequency "hockey-stick" epicardial probe is very helpful when imaging very small structures, typically the coronary arteries. As advances in 3D echocardiography have occurred, experience with intraoperative 3D imaging in congenital heart disease has evolved, both epicardial and TEE Simpson et al. (2017). The ability to have all these probes readily available is important to be able to optimally provide imaging and information back to the team. In order to conduct epicardial imaging directly on the heart or vessels in a sterile fashion, the operating room assistants usually have a sterile sleeve or "condom" like cover in which the small surface probe can be inserted and protected Cyran et al. (1989).

While real-world experiences vary, published guidelines generally suggest that adult size TEE probes can be used for pediatric patients over 20 kg. Pediatric TEE probes are selected for smaller patients down to about 3–3.5 kg Zyblewski et al. (2010). Below that, the micro-mini TEE probe can be attempted, which may enable imaging in the patient that is approximately 2–3 kg Stevenson & Sorenson (1993), Toole et al. (2015).

Epicardial imaging is generally performed with the smallest foot-print pediatric probe that is available and will fit in the very small and crowded area of a neonatal or infant sternotomy space. Epicardial imaging is typically performed in tandem with the surgeon, with the surgeon holding the probe (in a sterile sleeve) and the imager optimizing imaging parameters, acquiring clips, and helping to interpret the imaging Dragulescu et al. (2012). In the older, larger pediatric patient, sometimes downsizing to the next lowest frequency transducer is chosen given there is more space, and when the imager believes the tradeoff for a lower frequency transducer is acceptable in order to achieve increased penetration of the cardiac structures and myocardium. Epicardial imaging is commonly superior and typically complementary to TEE imaging when evaluating coronary and branch pulmonary arteries De Castro et al. (2006).

Case Vignettes

Below are three selected case examples of different pediatric congenital cardiovascular patients (and lesions) who underwent operative repair, including select corresponding echocardiographic images from the operating room (preoperative and/or postoperative) in order to provide a visual sampling of the role of echocardiography in the operating room and in the care of the pediatric congenital cardiac patient.

Case 1: VSD

10 month old with a large conoventricular VSD and heart failure/poor growth: In general, VSDs are fairly straightforward lesions for both the imager and the surgeon. It is important to be descriptive, however, including the type/location of the VSD, presence of additional VSDs, and additional associated lesions, such as an ASD or a PDA Cohen & Stevenson (2007). Once the preoperative anatomy is confirmed and the operation is undertaken, the postoperative interrogation after weaning from cardiopulmonary bypass should include demonstrating a well-anchored VSD patch by 2D imaging. Color

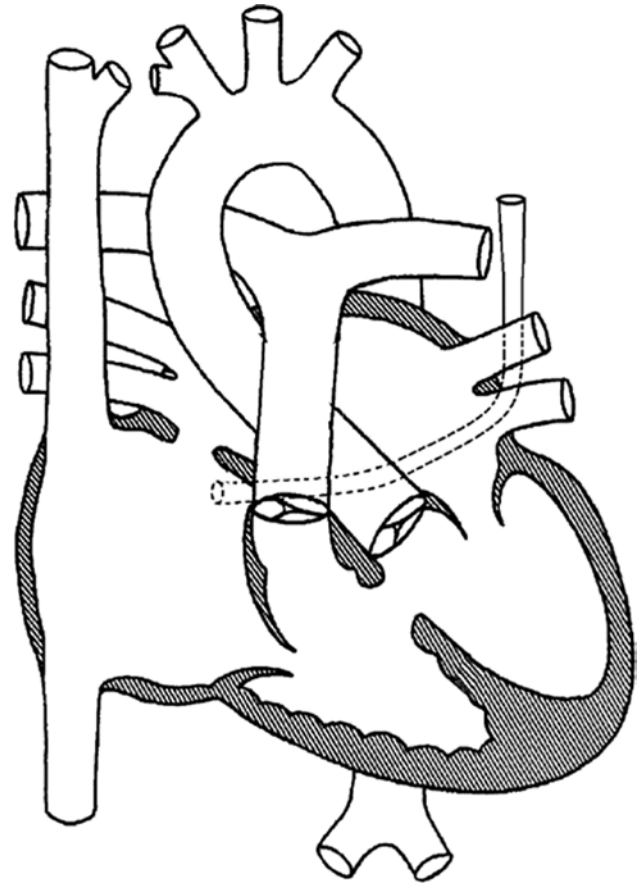

Fig. 1 Preoperative "valentine" diagram demonstrating VSD. Note, there is also a persistent LSVC to coronary sinus—a systemic venous variant that can be found in isolation or in combination with other congenital cardiac disorders

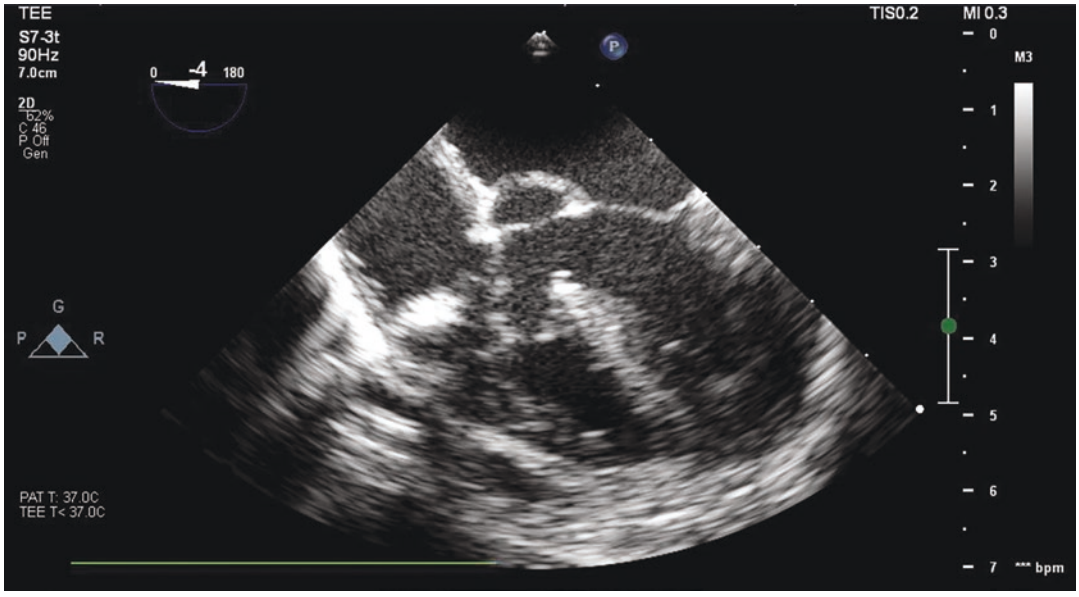

Fig. 2 Preoperative TEE 4 chamber view demonstrating the VSD

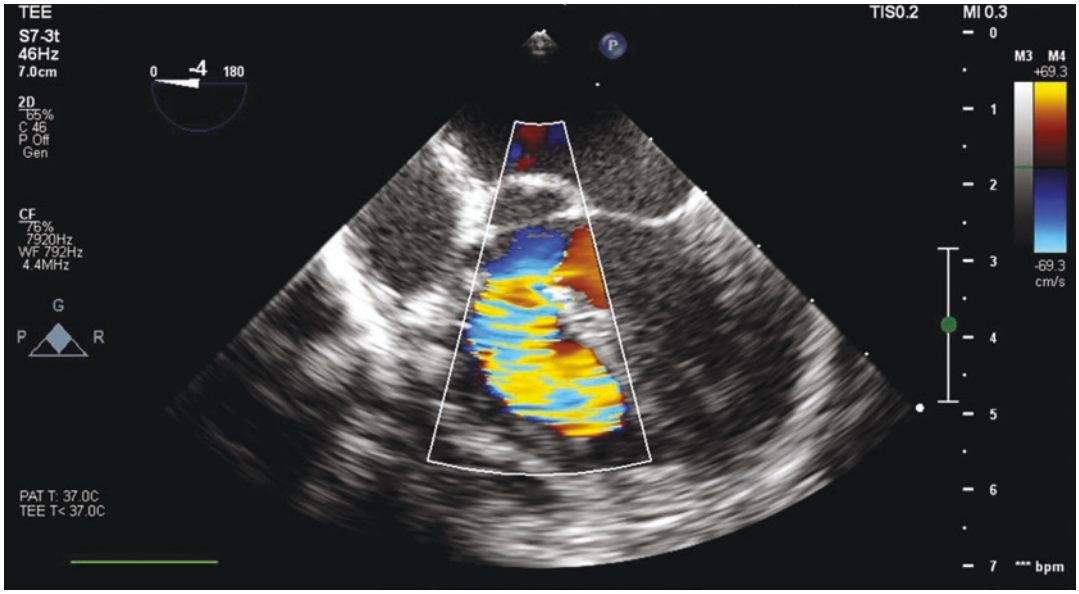

Fig. 3 Preoperative TEE 4 chamber view, similar to Fig. 2, with the addition of color Doppler mapping, demonstrating left to right VSD flow

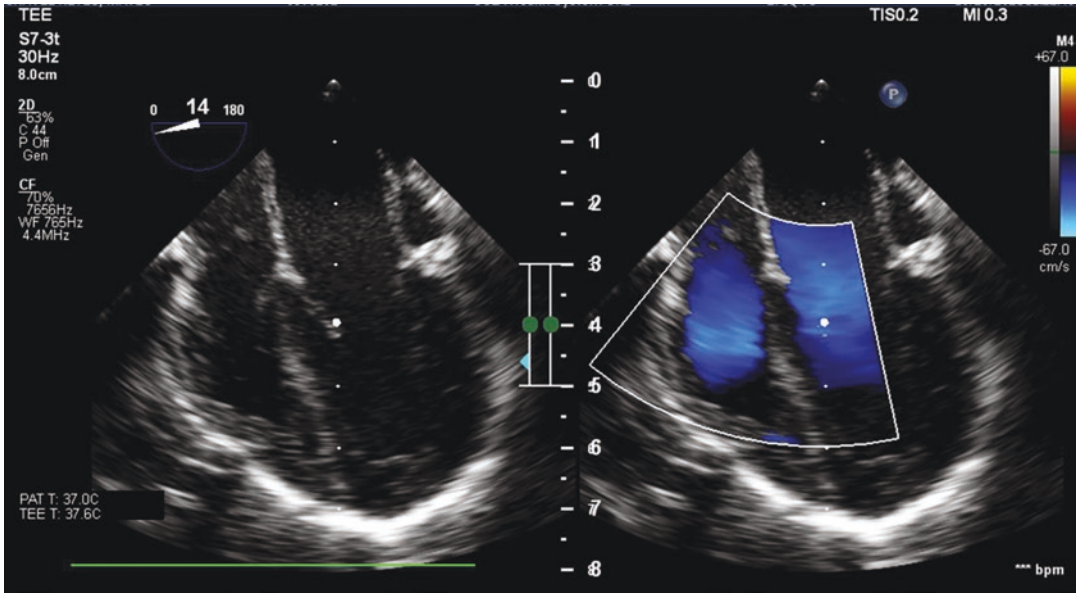

Fig. 4 Postoperative 4 chamber view, which on initial interrogation does not reveal an obvious residual VSD

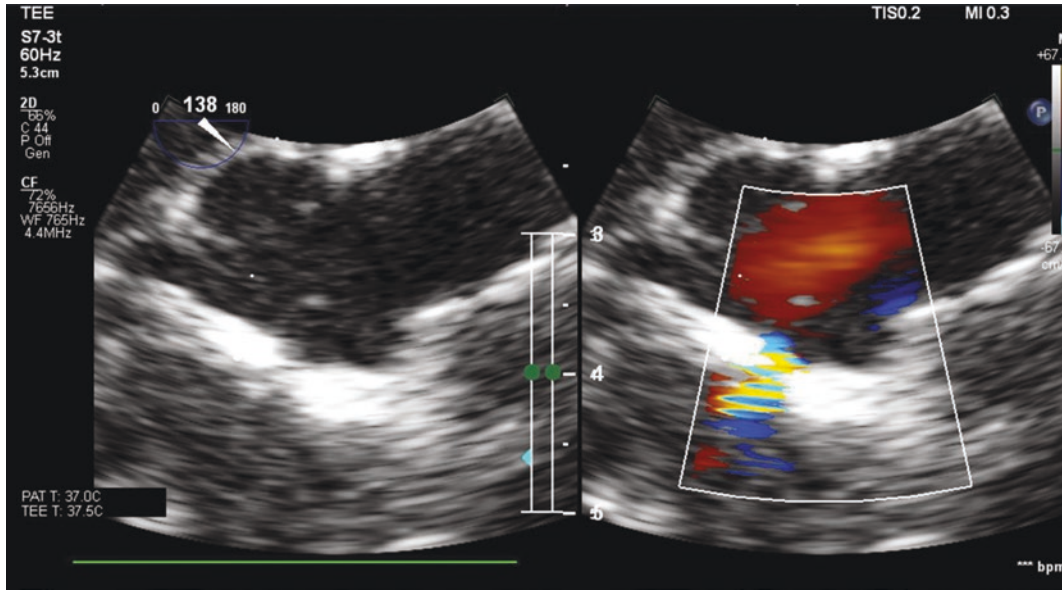

Fig. 5 Modified sagittal, zoomed-up view, demonstrating the aortic valve and VSD patch (bright linear structure), which unlike the 4 chamber view, reveals a small residual patch leak seen by color Doppler mapping (blue jet)

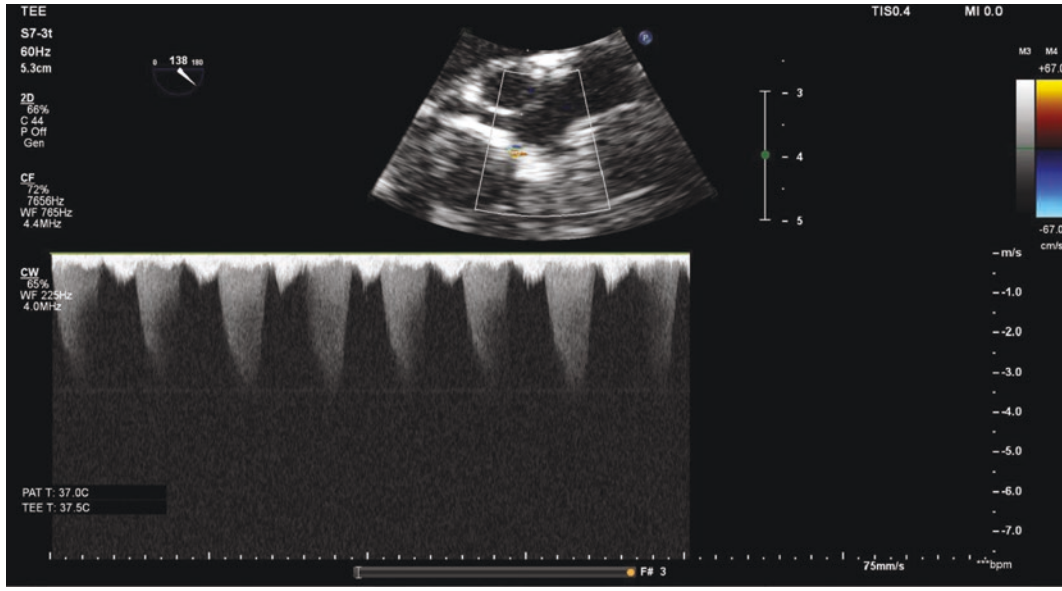

Fig. 6 Continuous wave Doppler recording through the residual VSD jet identified in Fig. 5. Note the high velocity, which is consistent with the expected low RV systolic pressure following VSD closure

Doppler mapping of the margins of the patch and septum should be provided at the appropriate color scale so that a residual VSD patch leak can be identified. RV systolic pressure by TR jet Doppler is helpful to show if there is adequate TR present. Most VSDs operated upon are large and unrestrictive, and so, the RV systolic pressure is systemic on preoperative imaging, but not after repair (Figs. 1, 2, 3, 4, 5 and 6).

Case 2: ALCAPA

5-week-old infant with ALCAPA who presented with a concurrent viral infection and respiratory failure. Mechanical ventilation and IV cardiac medications were instituted and after a brief period, the patient underwent repair. In the case of ALCAPA, it is not uncommon that the patient has myocardial failure with very little left ventricular systolic ejection and the patient may even be on ECMO support. In addition, the coronary arteries are very small structures in infancy (a common time-frame for ALCAPA presentation), in the order of a couple of millimeters, and so these lesion-specific patient factors can make for very challenging echocardiographic imaging in the operating room. It is important the imager in such a case has demonstrated where spatially the LCA arises from the PA, and as mentioned, the status of myocardial function. Associated lesions, such as MV regurgitation, ASD, PDA, or other findings should be discussed. Often, these patients will not be able to wean from bypass and will remain on mechanical support (ECMO), making postoperative imaging additionally challenging. Typically, epicardial imaging with the highest frequency transducer will provide the best imaging to interrogate the repair. This should include direct 2D imaging of the coronaries themselves, as well as color Doppler mapping and pulse wave Doppler velocity recordings.

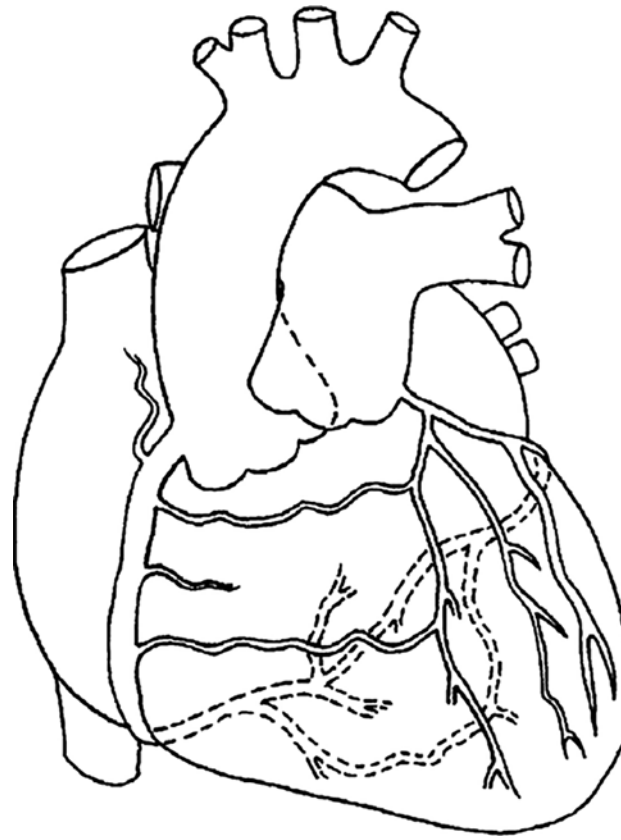

Fig. 7 Preoperative "valentine" diagram demonstrating ALCAPA. Note the dilated right coronary artery and the collateralization present between the coronary arteries

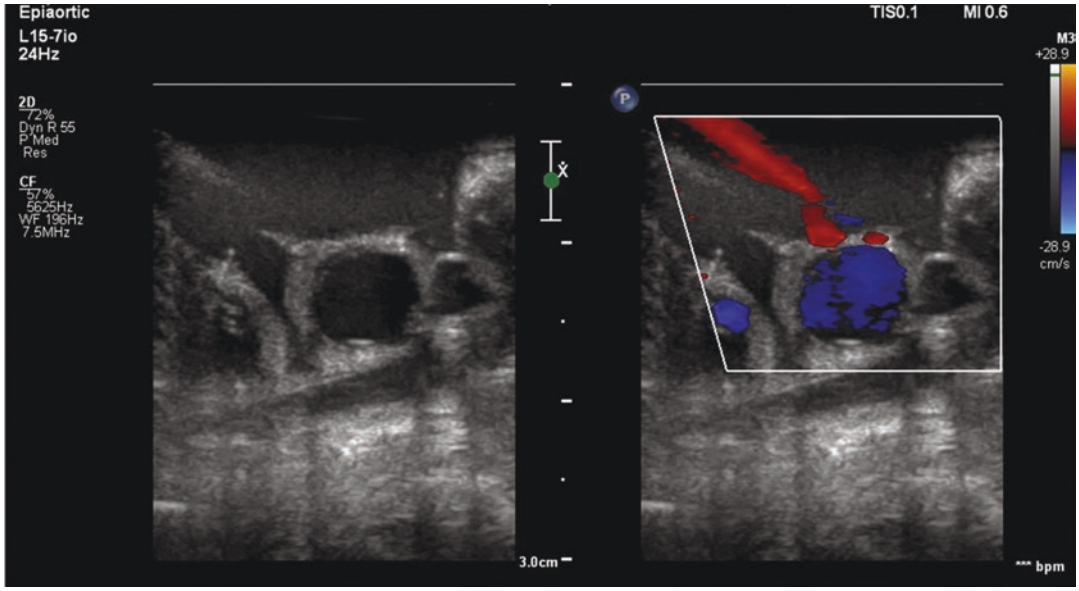

Fig. 8 Intraoperative epicardial imaging with the high frequency, linear array "hockey-stick" probe demonstrating RCA patency and low-velocity, antegrade flow Xing et al. (2002)

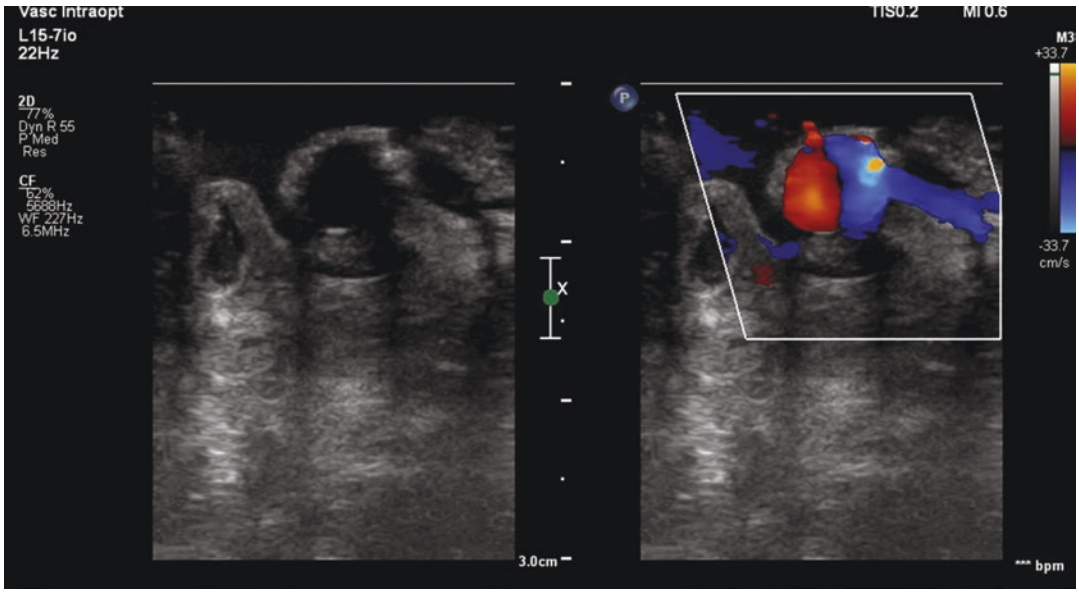

Fig. 9 Postoperative epicardial imaging of the left coronary artery system with the high frequency, linear array "hockey-stick" probe. The reimplanted and patched LCA appears patent with flow demonstrated into the proximal LAD and circumflex branches Stern et al. (2017)

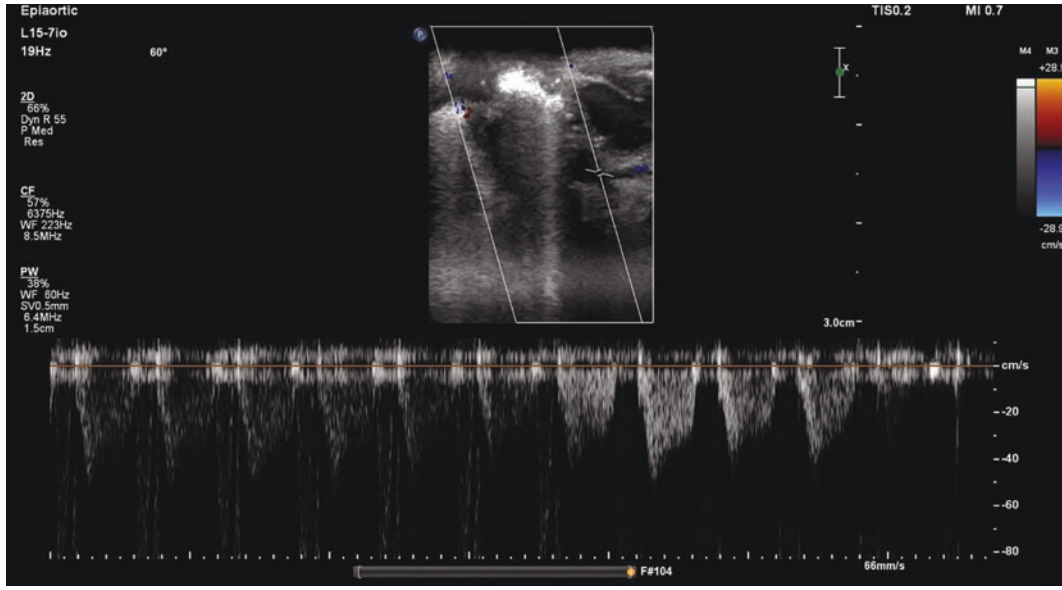

Fig. 10 Postoperative Doppler interrogation of coronary flow after ALCAPA repair using the high-frequency "hockey-stick" probe. The flow pattern is relatively normal with an acceptable peak velocity measuring ~40 cm/s

With this approach, the presence of residual or new narrowings or stenoses in the vessels can be optimally identified. TEE may show the take-off or portions of the coronaries, but there may be more-limited angles of interrogation in order to obtain the Doppler flow profiles. Generally speaking, epicardial imaging is superior to TEE imaging for most forms of coronary artery imaging and abnormalities, not only in ALCAPA repair (Figs. 7, 8, 9, and 10).

Case 3: Complete Transposition (D-TGA) Undergoing a Senning

6-year-old D-TGA with intact ventricular septum s/p neonatal balloon atrial septostomy complicated by a significant stroke s/p initial pulmonary artery band and no further interventions until the current palliative Senning repair. The patient also underwent pulmonary artery band take-down and reduction plasty of the pulmonary arteries—which had demonstrated severe aneurysmal dilation given the prolonged period of banding and ensuing poststenotic dilation. In this type of case, both TEE and epicardial imaging were used and are optimal to achieve the best echocardiographic interrogation after repair. While much of the Senning can be seen by TEE, epicardial echocardiography can provide additional, high-resolution interrogation of smaller areas, such as suture lines or hard to get to portions of the baffle path-

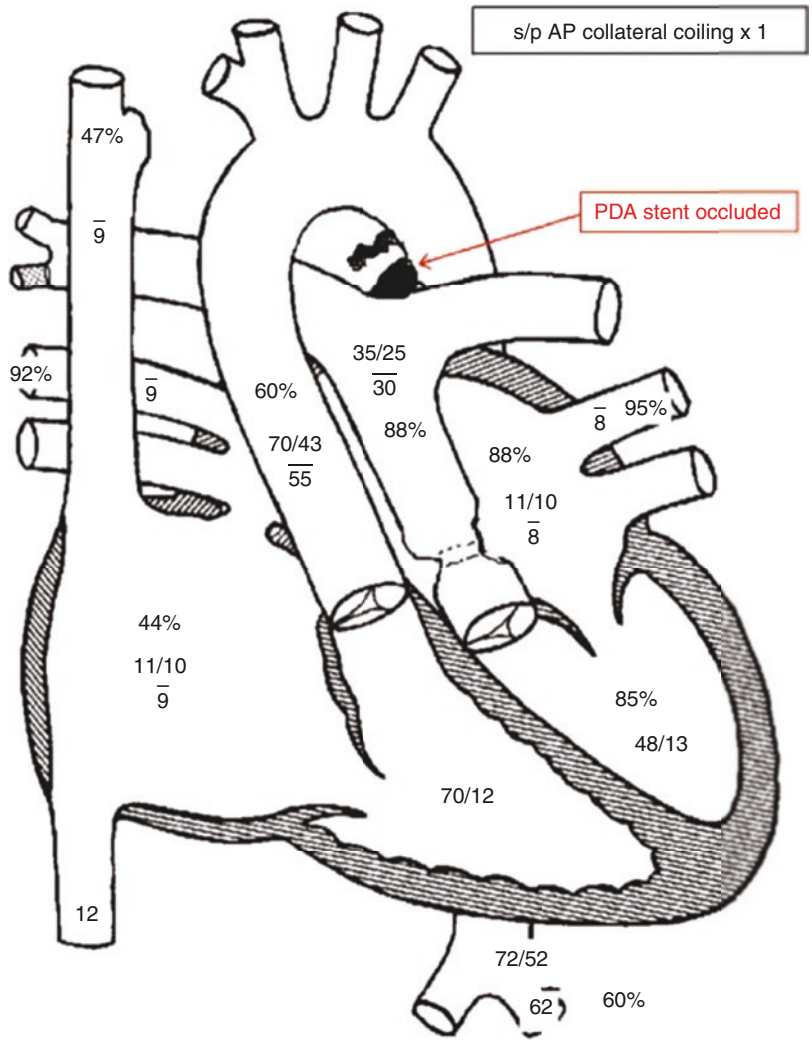

Fig. 11 Preoperative "valentine" diagram demonstrating D-TGA/intact ventricular septum s/p pulmonary artery banding. Not depicted in the diagram is the severe aneurysmal dilation of the main and branch pulmonary arteries

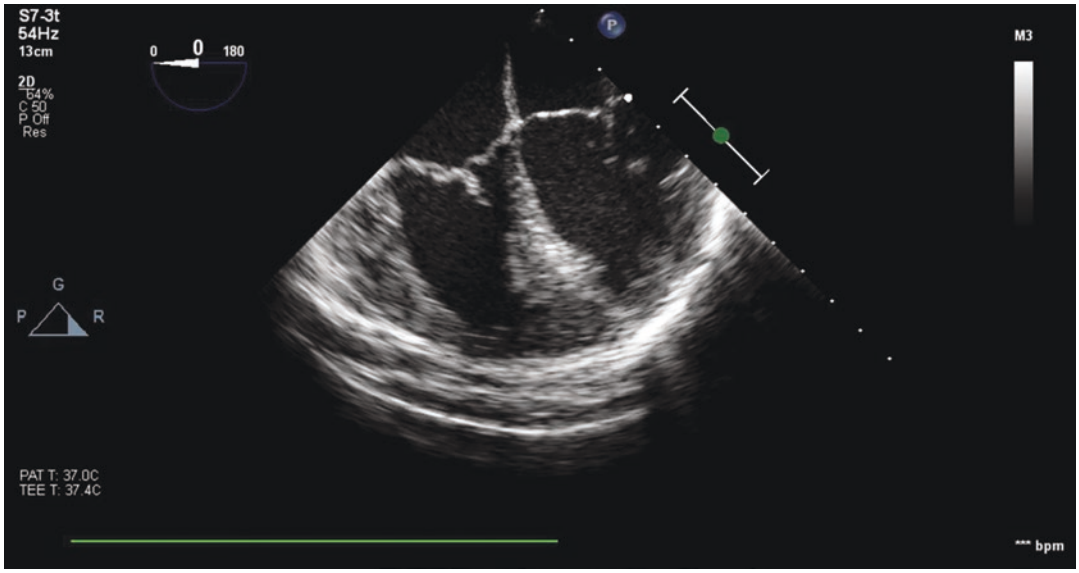

Fig. 12 Preoperative TEE, 4 chamber view, providing a somewhat misleading sense that no CHD is present. Note both ventricles are apex formed and no obvious VSD is seen. The transposed great arteries cannot be seen in this view, which is obtained posterior within the heart at the level of the atrioventricular valves, and does not include the more anterior outflow tracts or semilunar valves

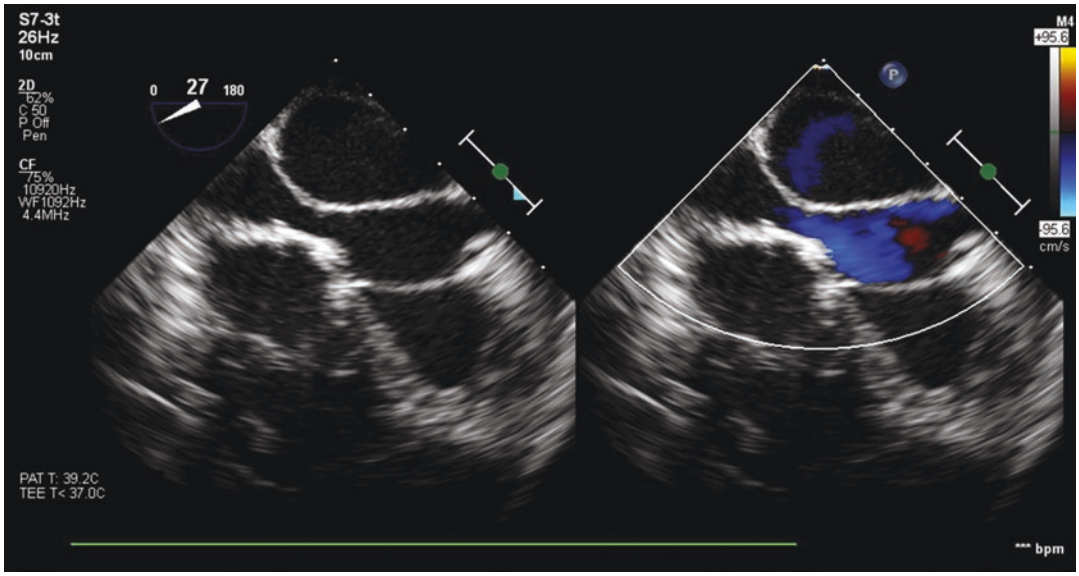

Fig. 13 Postoperative TEE after the Senning operation, demonstrating new intra-atrial baffle pathways (curved linear, echo bright structure) not seen in the prior image (Fig. 12). On the left (2D), and with superimposed color Doppler mapping, on the right. The color Doppler mapping is demonstrating a patent pathway from the right-sided caval limbs toward the left AVV and morphologic left ventricle, which is the subpulmonary ventricle. As well, above the baffle is a space that represents a portion of the pulmonary venous pathway, in which the left-sided pulmonary venous flow is directed to the right-sided tricuspid valve and systemic ventricle

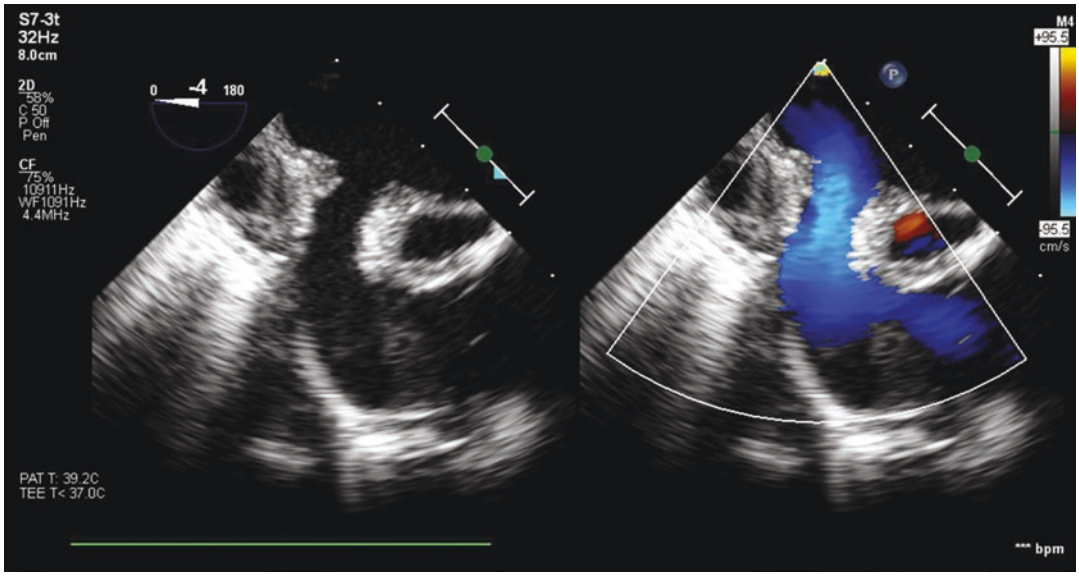

Fig. 14 Postoperative TEE demonstrating patency and flow in the pulmonary venous baffle. By 2D and color Doppler mapping, the pathway appears widely patent with low velocity, non-aliasing antegrade flow, directed toward tricuspid valve and systemic right ventricle

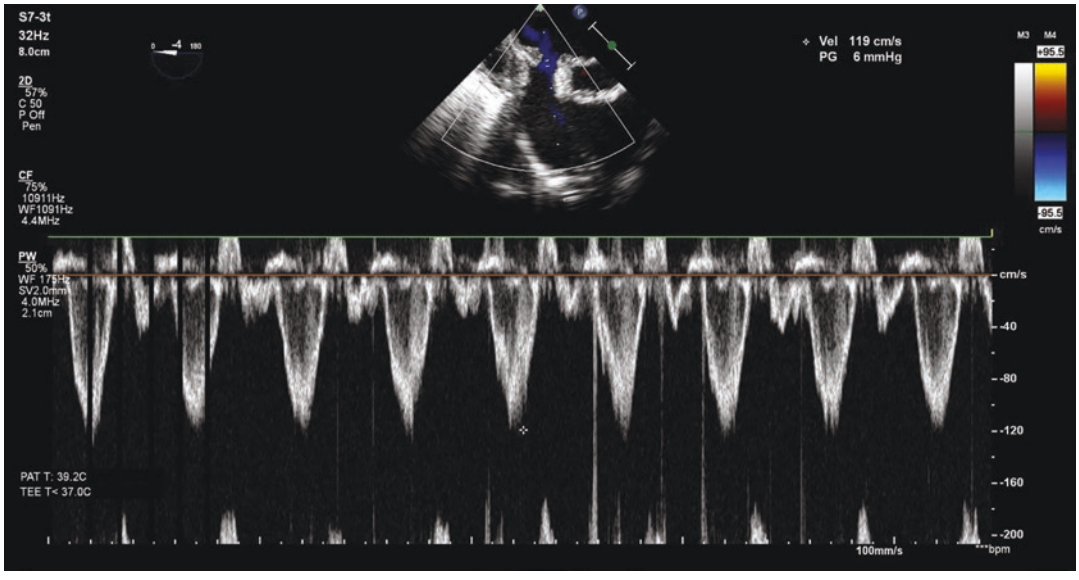

Fig. 15 Postoperative TEE, pulse wave Doppler recording in the same view as above (Fig. 14) demonstrating low-velocity flow, and a minimal mean gradient (now shown) in the pulmonary venous baffle pathway

ways. It was also helpful, in this case, to image the length of the pulmonary arteries given their massive dilation and downsizing plication surgery that was performed. Not only was the MPA involved, but the branch pulmonary arteries were as well. TEE can be limited in imaging the entire length of the branch pulmonary arteries and so epicardial imaging, in general, and in this case, was helpful in seeing the slightly more distal portions of the branch pulmonary arteries (Figs. 11, 12, 13, 14 and 15).

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3D Printing and Modeling of Congenital Heart Disease for Pre-Surgical and Pre-Procedural Planning

Gregory Perens and Jure Marijic

Abstract

Standard of care imaging for anatomy and function of congenital heart disease is 2-dimensional echocardiography, with the addition of axial CT and MRI for specific lesions. While 3-dimensional (3D) echocardiography has improved and has value for specific anatomy such as atrioventricular valves, it is limited to transthoracic imaging and by lower frame rates that are not optimized for children with higher heart rates. Cardiac CT and MRI images can be reconstructed into 3D images for complete visualization of congenital heart structures that are important for interventional catheter and surgery procedures. Virtual and 3D printed heart models created from blood pool contrast-enhanced images have become a more frequently used and important tool to plan for the most complex cases. Although 3D printed patient-specific heart models have limitations, their use has become a valuable tool for education, testing catheter-based devices, and planning complex congenital surgeries.

Keywords

3D printing · Congenital heart disease Virtual reality · Catheterization · Cardiac surgery

Introduction

Three-dimensional (3D) imaging has revolutionized the care of patients with congenital heart disease. The 3D printing of congenital heart disease models from advanced computed tomography (CT) and magnetic resonance imaging (MRI) imaging is an additional tool that is used to improve planning, and safety for the patients with congenital disease undergoing invasive procedures. 3D printing is more and more widely used to gain a better understanding of complex heart anatomy prior to surgical and catheter interventional procedures. 3D heart models are created with a process that starts with information from blood pool contrast-enhanced multidimensional images of the heart and vessels. Usually, the contrasted blood pool is selected, or "segmented," and this creates a 3D computer model, that is hollowed and sent to a 3D printer. The inside of the hollow model represents the endocardial surface and inner walls of the vessels. The

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model represents what the surgeon will view inside the heart at the time of surgery, and where devices, valves, or stents would be placed within the heart. In some cases, myocardium and surrounding tissue can be incorporated into the model. To allow for the most realistic simulation and comparison of the size of the device, and the valve and to allow for deployment simulation, 3D models are usually printed as a 1:1 size representation of the actual structures obtained from the imaging. End-diastole images are usually chosen as the best representation of what the surgeon will view during surgery (Yoo et al. 2021). Specific end-diastolic imaging may be a challenge when only one-time point in the cardiac cycle is imaged. Multiphase CT imaging and advanced cardiac MRI imaging modalities are now able to create 4-dimensional heart images, even in the smallest patients (Nguyen et al. 2021).

3D Printing Process

The creation of a 3D model of the heart and blood vessels requires high-quality source data from advanced multiplanar cardiac imaging, either electrocardiogram-gated, contrast-enhanced CT, or MRI. The contrast should have similar signal intensity throughout the blood pool region of interest, ideally with multiphasic imaging through the cardiac cycle. The choice of imaging modality depends on the cardiac lesion, patient age, institutional preference, imaging capabilities, consideration of radiation dose, and anesthesia requirements. The fidelity of the final printed model depends heavily on the quality of the source images. It is important to have clear images, without motion artifacts, thin slices, and relatively equal contrast throughout the blood pool. If the inclusion of the myocardium is desired as part of the model, this is also possible, depending on the imaging fidelity.

The process begins with uploading imaging data files to segmentation software. The contrast-enhanced blood pool is semiautomatically selected based on its signal intensity compared to surrounding structures. Unnecessary surrounding structures and artifacts are removed, and any additional structures can be manually traced and added. This process generates a 3D virtual model of the blood pool within the heart and vessels. Further editing creates a thin, smoothed shell around the blood pool.

The computer-generated 3D model is uploaded to a 3D printer's software program and set on a virtual printing bed in optimal orientation. Supporting structures are added that are printed along with the model between the print bed and anatomic parts that would otherwise be printed free floating. Once printed, the model requires postprocessing to remove the support material. In the case of more advanced SLA (stereolithograph apparatus) and polyjet printers, further processing is usually required. The entire process can take anywhere from a few hours to a few days, depending on the quality of the source images, complexity of the anatomy to be segmented, size of model to be printed, and amount of postprocessing of the print. The main steps in the process of 3D printing from CT and MRI images are shown in Fig. 1.

Different types of 3D printers exist with varying printing mechanisms, costs, materials, and fidelity. The most common types of printers used include fused filament fabrication (FFF), SLA laser, and high-end polyjet. FFF and SLA can in general print one or two color and material at a time, while polyjet has the ability to lay down curable liquids in microscopic layers that can use multiple colors and materials. Hard materials are inexpensive and easier to print, however they cannot be manipulated and are less useful for device testing. Flexible, elastic materials are superior and provide more realistic device testing, but are more challenging to print on all but the high-end printers.

In the remainder of this chapter, we will present several examples in which we used 3D printing to plan and simulate the surgery or intervention to successfully treat patients.

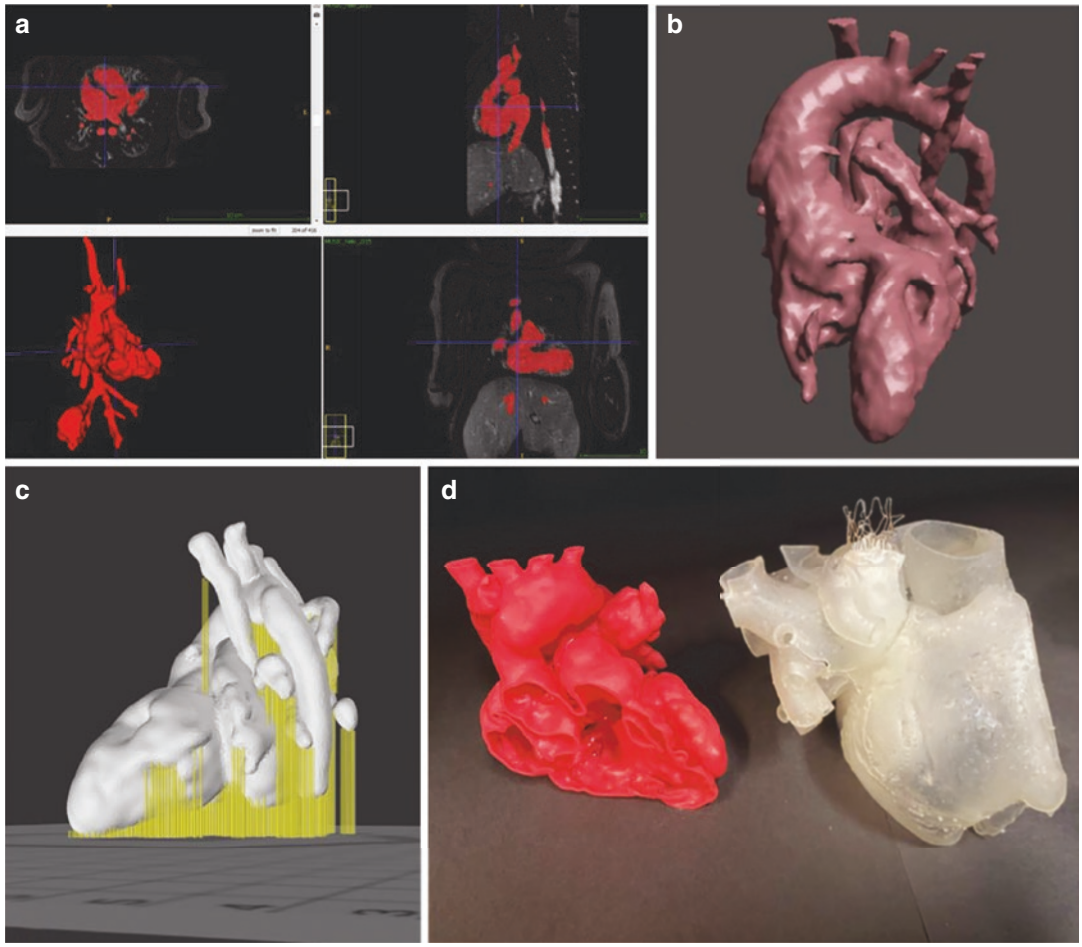

Fig. 1 3D printing process. (**a**) Segmentation of contrast-enhanced cardiac MRI. (**b**) Virtual blood pool heart model created from segmentation. (**c**) Model on virtual printer bed with supports (yellow), ready to send to printer. (**d**) Printed congenital heart models: hard model of double outlet right ventricle (red), and partial anomalous venous return printed of flexible material, with stent placed within superior vena cava

Double Outlet Right Ventricle

Double outlet right ventricle (DORV) encompasses a heterogeneous group of congenital heart defects that have in common that both great vessels arise completely or predominantly from the right ventricle. DORV represents a unique and complex anatomy such that visualization of a 3D representation of the heart can significantly assist in the preparation and execution of the surgical plan (Yoo and van Arsdell 2018; Garekar et al. 2016). Hearts classified as DORV have multiple subtypes based on anatomy and physiology. The main surgical question to be answered for DORV using 3D models is whether the heart may undergo septation creating a biventricular repair or anatomy that requires single ventricle palliation with a Fontan procedure. In the double outlet right ventricle, both great arteries and semilunar valves arise in the majority from the right ventricle. However, there can be various arrangements of the aorta and pulmonary artery in relation to the ventricular septal defect (VSD). It is these great artery relations in double outlet right ventricle that will create physiology consistent with that of either Tetralogy of Fallot, VSD, transposition of the great arteries, or single ventricle physiology.

A 3D model of a DORV heart allows the surgeon to assess critical anatomic components and create a surgical plan. The surgery will need to result in blood flow from the left ventricle (LV) to the aorta. This can create problems within the right side of the heart and for the LV outflow tract. 3D visualization helps one predict if VSD closure will create obstruction to tricuspid inflow, if overall RV size and volume will be significantly reduced, and if the VSD needs to be enlarged to provide unobstructed LV outflow to the aorta. Other considerations for the repair of DORV hearts are obtained from CT or MRI and echo and include coronary artery anatomy that is critical in cases that may require arterial switch; potential valve tissue straddling the VSD that could obstruct the flow of blood to the aorta from LV through VSD; abnormal valve function that could require repair or compromise postoperative heart function; and ventricular volumes in cases of borderline size ventricles that would preclude the use of both ventricles. Figures 2 and 3 demonstrate a case of DORV with subpulmonary VSD with the aorta further rightward.

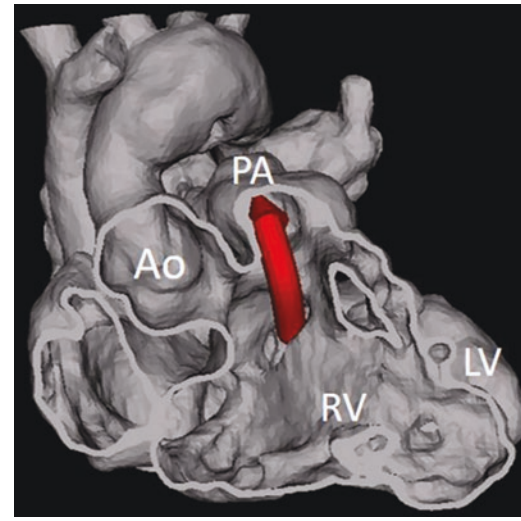

Fig. 3 Double outlet right ventricle heart case in Fig. 1, with the right ventricular free wall removed. The red arrow demonstrates flow through the VSD from the LV to the pulmonary artery. To achieve a biventricular repair, an arterial switch was performed to bring the aorta in proximity to the VSD. A patch is placed from the inferior crest of the ventricular septum up to the neo-aorta to separate oxygenated and deoxygenated blood flows and baffle the LV flow to the neoaortic valve

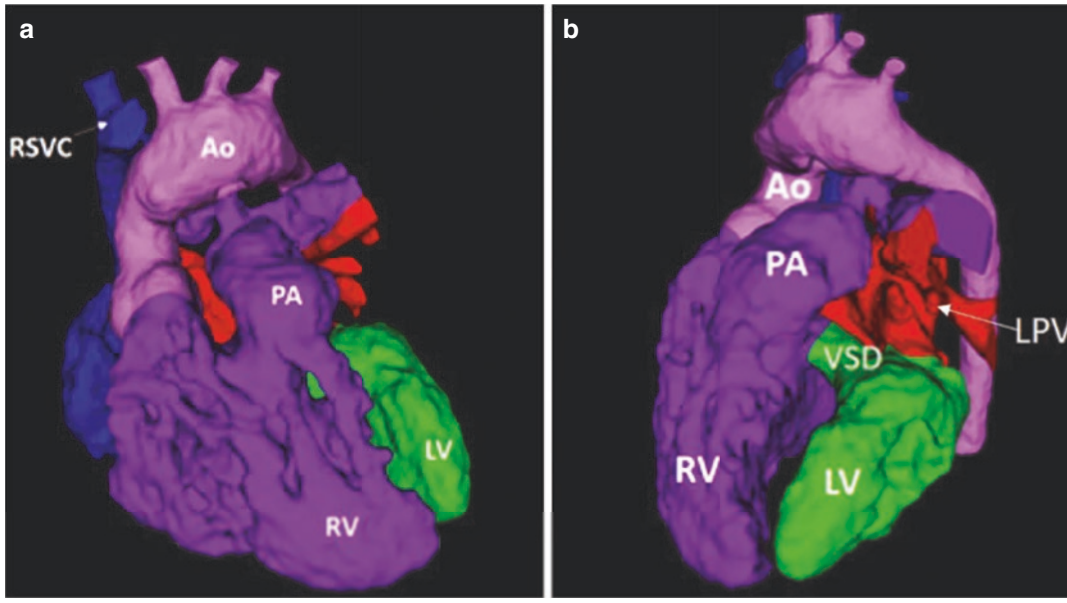

Fig. 2 Six-month-old with double outlet right ventricle. The aorta and pulmonary artery arise fully from the right ventricle and are transposed (**a**). The VSD is sub-pulmonary (**b**), and the aorta is malposed further rightward. To achieve a biventricular repair, an arterial switch was performed to bring the aorta in proximity of the VSD. Then a patch was placed to baffle LV flow through the VSD to the aorta. *Ao* aorta, *LV* left ventricle, *LPV* left pulmonary veins, *PA* pulmonary artery, *PV* pulmonary vein, *RSVC* right superior vena cava, *VSD* ventricular septal defect

Abnormal Venous Connections

Heterotaxy, or "other arrangements," comprises a set of CHD with various abnormal organ and vessel arrangements, often with intracardiac abnormalities. Abnormal venous anatomy, both pulmonary and systemic, may have abnormal arrangements requiring surgical intervention as part of biventricular repairs and single ventricle palliations. To achieve a biventricular repair, some hearts may need routing of abnormally arranged venous connections to the correct ventricle. This usually means the routing of the venous blood flows within the atria similar to the atrial switch (Senning or Mustard procedure) previously used for the repair of transposition of the great arteries (McElhinney et al. 1996; Kuwahara et al. 2020). Venous abnormalities in heterotaxy may include ipsilateral pulmonary vein connections, bilateral superior vena cava, interrupted inferior vena cava (IVC) with azygous continuation, or an IVC draining to the left atrium. The atrial baffle required for these cases can be unique and more complex than a standard atrial baffle, such that 3D models of these hearts can help plan the baffle route within the atrium. A complex case with abnormal systemic and venous anatomy that used preoperative planning with a 3D model is shown in Fig. 4.

For cases undergoing single ventricle palliation with a cavopulmonary connection (Glenn shunt) and Fontan, systemic veins are routed surgically to the pulmonary arteries, via an extracardiac conduit or as a lateral tunnel using part of the atrium. For patients with heterotaxy and abnormal venous anatomy, the Fontan conduit may require alternative routing to avoid compressing pulmonary veins. In certain circumstances, a standard Fontan conduit will likely not create equal blood flow to both pulmonary arteries, due to stenosis between the branch pulmonary arteries, or pulmonary hypertension or AVMs within one lung. It is important to get hepatic blood flow to both lungs to prevent the development of pulmonary AVMs. In some of these cases, routing of the IVC/hepatic blood to both pulmonary arteries with the use of a bifurcated, Y-shaped extracardiac conduit may be used to ensure equal or near equal distribution of hepatic flow and also reduce energy loss.

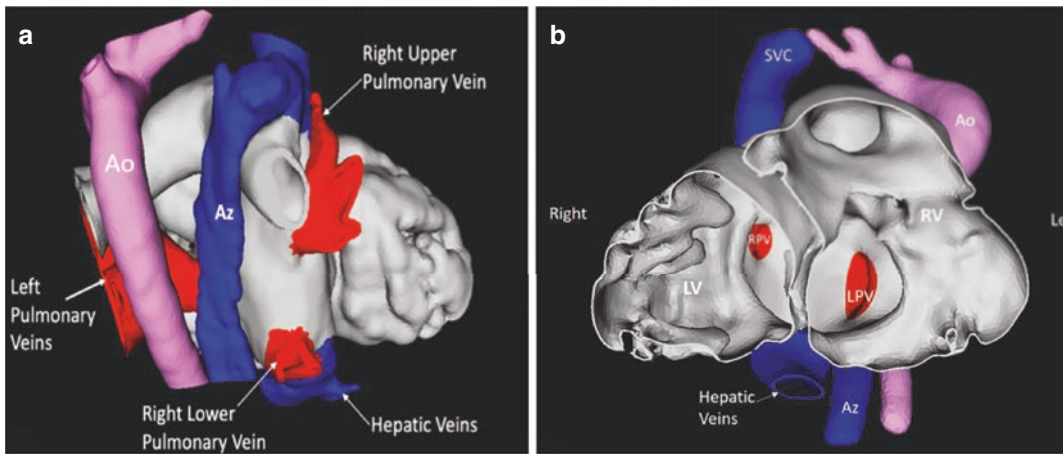

Fig. 4 3D virtual model created from cardiac MRI. Three-year-old with heterotaxy syndrome, interrupted inferior vena cava with azygous continuation, ipsilateral pulmonary vein drainage, and L-looped ventricle orientation (left ventricle to the right of morphologic right ventricle). (**a**) Posterior view showing both right pulmonary veins and the systemic veins draining to the right atrium. The left pulmonary veins drain normally to the left atrium. (**b**) Anterior coronal view with ventricle mass removed showing corresponding ventricular inflows. A complex atrial baffle was performed so that the pulmonary veins drained rightward to the left ventricle, while the systemic venous flow was directed to the left-sided right ventricle. *Ao* aorta, *Az* azygous vein, *LPV* left pulmonary veins, *LV* left ventricle, *RPV* right pulmonary vein, *RV* right ventricle, *SVC* superior vena cava

Hybrid Surgery and Catheterization Procedures: Closure of Complex Ventricular Septal Defects

VSDs are among the most common CHD diagnoses requiring surgical intervention. If the VSD is large, causing significant overcirculation of the cardiopulmonary system and resulting in symptoms or poor patient growth, then it will need to be closed. Alternatively, a band may be placed around the main pulmonary artery to restrict flow and allow the child to grow prior to VSD closure. Most VSDs only require echocardiography for preoperative assessment. This includes VSDs of the perimembranous, muscular, and outlet types, and atrioventricular septal defects. While most VSDs are closed surgically, a growing number of perimembranous and muscular defects are closed in the interventional cardiac catheterization lab by deployment of a closure device (Escobar et al. 2021; Mendez et al. 2018; Bhatla et al. 2017). Printing realistic 3D models can assist in decision making about feasibility of device closure as well as choice of the device that is used for closure.

Some rare VSD subtypes may require advanced cardiac imaging with CT or MRI for full understanding of the defect size and surrounding structures. From the advanced images, a flexible, soft 3D model of the heart can be used to determine the RV entry site and the best angle for the catheter approach. Various device sizes and shapes can be tested within the model. The actual procedure is done with a beating heart, and off bypass. Anesthesia care may be more involved with these cases due to potential risk of arrhythmias during catheter manipulation, impairment of RV filling, deformation of tricuspid valve and/or mitral valve causing tricuspid or mitral insufficiency, hypotension, and bleeding. Testing of a VSD closure device within a soft 3D model and the procedure are demonstrated in Figs. 5 and 6.

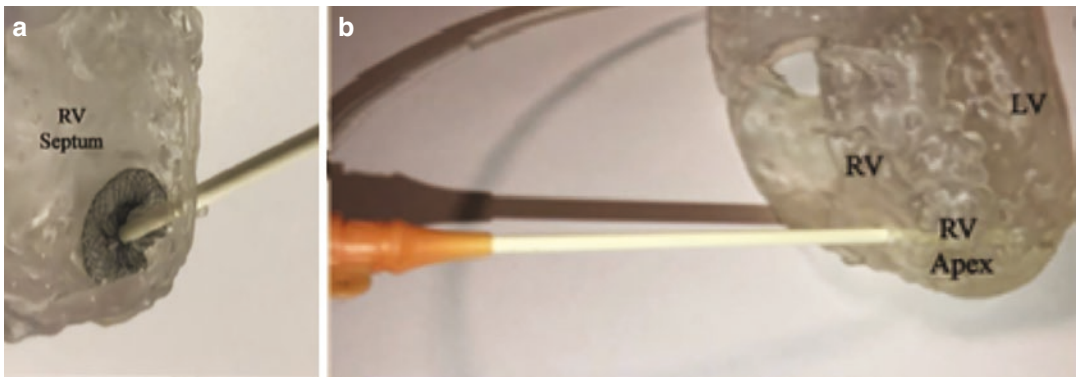

Fig. 5 6-month-old with an apical VSD that underwent hybrid device closure of the defect. (**a**) Amplatzer muscular septal occluder (Abbott Cardiovascular, MD, USA) attached to catheter, placed through the right ventricular wall of a patient-specific heart model into the VSD; right posterior view. (**b**) Anterior superior view

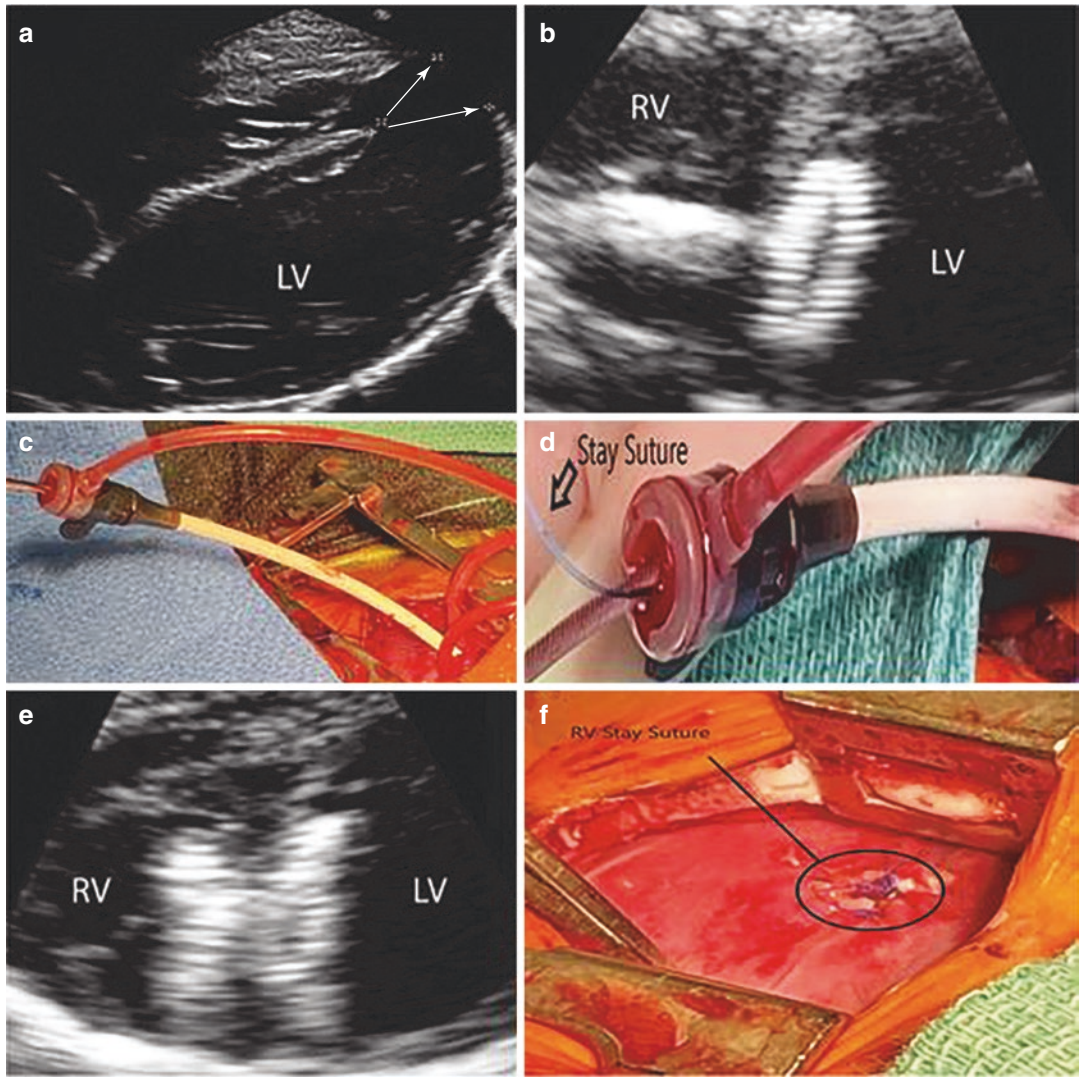

Fig. 6 Hybrid device closure of apical muscular VSD in 6 month old. (**a**) Transthoracic image of apical VSD that measured 8 mm (arrows). (**b**) Transesophageal echo (TEE) image of catheter placed from RV free wall across the VSD with the first disk deployed within LV. (**c**, **d**) Small central thoracotomy performed to access RV free wall. The catheter is directed into the RV free wall and across the VSD. (**e**) Final TEE imaged of Amplatzer device (Abbott Cardiovascular, MN, USA) with disks on either side of the VSD. (**f**) A small incision in the RV free wall is closed, and a suture is sewn to ensure that there is no postoperative bleeding from the site of the RV entry during the device deployment

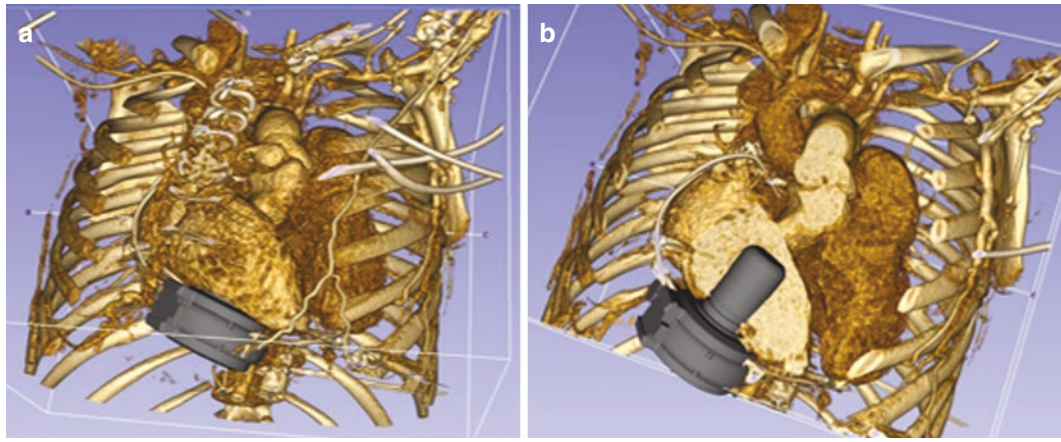

Fig. 7 Three-dimensional rendering of contrast-enhanced CT scan of 25 year old that had undergone an atrial switch procedure for transposition of the great arteries. The systemic sub-aortic right ventricle had failed, necessitating the use of a VAD as a bridge to heart transplant. A 3D model of a centrifugal flow VAD is virtually placed within the right ventricle apex (**a**), and the inflow cannula shown within the RV cavity, (**b**)

Ventricular Assist Devices and Heart Transplantation

The innovation in the design of the ventricular assist devices (VAD) has dramatically improved the outcomes and expanded options for patients with end-stage heart failure. Due to the smaller size of pediatric hearts and other anatomical constraints, the placement of ventricular assist devices (VAD) within a failing ventricle may not be feasible or may need modification of technique and location of cannula insertion for complex congenital hearts with abnormal anatomy or significant hypertrophy that reduces ventricular chamber size. Unique locations for VAD placement may be "tested" within a 3D printed heart or by using a virtual VAD model within a 3D rendering of the CT or MRI (Miller et al. 2020; Farooqi et al. 2016; Barabás et al. 2019). This can help determine the optimal location within the chest and point of entry into the heart such that the VAD inflow sits best within the failing ventricle cavity and to prevent inflow or outflow graft kinking or obstruction, graft pressure on the mediastinal structures, or the chest wall. For optimal use of the 3D prints, a full heart including the muscle is ideal. Examples of abnormal anatomy where preimplantation planning could be helpful include heterotaxy with abnormal venous or ventricular arrangements, dextrocardia, single ventricle hearts, and previously repaired congenital heart disease. A case of an adult with transposition of the great arteries repaired with an atrial switch and requiring a VAD for the failing systemic right ventricle is shown in Fig. 7.

Limitations of 3D Virtual and Printed Hearts

3D heart models created from advanced imaging have a few important limitations. A single model is a representation of the heart at one specific time point in the cardiac cycle. The model most often is chosen to represent the relaxed state during diastole. However, if only a single-phase time point is imaged by CT or MRI, the heart chamber sizes, outflow tracts, and septal defects may underrepresent their largest, true size (especially if the images are at end systole). Thus, multiphase imaging, if available is critical for optimal 3D heart models. Since the 3D models are created most often from the contrasted blood pool, steady-state enhancement of all cardiac structures and vessels will make for the best models and the least amount of time creating them. Newer advancements in cardiac MRI imaging have made steady-state blood pool imaging pos-

sible (Nguyen et al. 2021). Even with the best imaging, valve tissue is usually not imaged well enough, especially in pediatric patients, to be included in 3D models. This is true for the coronary arteries in many cases as well. These are important structures and an understanding of their anatomy and function usually still must be taken from echocardiography. Thus, the 3D model adds to the overall understanding of a congenital heart lesion, standard imaging modalities remain the foundation.

In conclusion, complex congenital heart disease 3-D printing can assist in the planning and delivery of care in patients with complex congenital heart disease. 3D printing augments cardiac care by allowing for planning, simulation, and education of potential surgical interventions and catheter-based procedures.

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Perioperative Imaging in the Adult Congenital Cardiac Patient

Gentian Lluri and Jeannette P. Lin

Abstract

Advances in medical therapies, diagnostic modalities, and interventional and surgical management have led to a decrease in mortality in the congenital heart disease (CHD) population with surviving adults now comprising most patients with CHD (Marelli et al., Circulation 115(2):163–172, 2007. Throughout their lives, adult congenital heart disease (ACHD) patients may require multiple surgical and interventional cardiac procedures. Given the complexity of CHD, knowledge of ACHD is required for perioperative transesophageal echocardiogram (TEE) evaluation or procedural transesophageal echocardiogram guidance. There have been several recent consensus statements and guidelines to address standardization of echocardiographic protocols to evaluate CHD via two-dimensional and three-dimensional transthoracic echocardiography (Di Salvo et al., Eur Heart J Cardiovasc Imaging 19(10):1077–1098, 2018, Li et al., Int J Cardiol 272:77–83, 2018; Simpson et al., J Am Soc Echocardiogr 30(1):1–27, 2017) and the American Society of Echocardiography (ASE) has published guidelines for performing a comprehensive TEE in pediatric and ACHD patients (Puchalski et al., J Am Soc Echocardiogr 32(2):173–215, 2019).

When obtaining a TEE, one should begin with a segmental approach to understand atrial situs, atrioventricular connections, and ventriculoarterial connections. Once the baseline anatomy and physiology have been established, a more detailed assessment of ventricular and valvular anatomy and function should be performed. It is very helpful to have echocardiographic protocols for each of the unique CHD diagnoses and common corrective surgical approaches, for example D-transposition of the arteries after atrial switch procedure. Such protocols can be built upon established guidelines on the above referenced guidelines (Puchalski et al., J Am Soc Echocardiogr 32(2):173–215, 2019). It is critical that echocardiographic reporting includes reference information on the initial defect, prior surgical management, hemodynamic state, and changes compared to prior imaging.

Keywords

Transthoracic echocardiography · Transesophageal echocardiography · Congenital heart disease · Imaging · Perioperative · Adult congenital heart disease

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Technical Considerations for Specific ACHD Lesions

Echocardiographic imaging of ACHD patients requires visualization of not only diagnosis-specific features but also their associated sequelae. Such sequelae may include ventricular dysfunction, chamber enlargement from shunts and regurgitant lesions, deterioration of conduits or prosthetic valves or pathologic native valves, and pulmonary hypertension. Three-dimensional (3D) echocardiography can be useful for valve and shunt assessment and is particularly important for interventional procedural guidance (Di Salvo et al. 2018; Li et al. 2018; Simpson et al. 2017; Puchalski et al. 2019).

The spectrum of ACHD conditions ranges from low- to high-complexity lesions. In low-complexity lesions such as an isolated secundum atrial septal defect (ASD), standard transesophageal views are usually adequate for identifying anatomy. In high-complexity lesions such as single ventricle anatomy, significant modifications of standard imaging views are often necessary to obtain all needed information. The classification of ACHD conditions remains dependent not only on the original defect at birth but also on the surgical management, which also has evolved over time. For example, a patient with d-transposition of the great arteries (d-TGA) after the older atrial switch procedure will require a significantly different approach to imaging than a patient with d-transposition of the great arteries after the newer arterial switch procedure. For clinical care, the 2018 ACC/AHA Guidelines on the Management of Adults with Congenital Heart Disease proposed a new anatomic and physiologic (AP) classification to succinctly understand a given patient's disease severity in a more comprehensive way (Stout et al. 2019). In this scheme, simple anatomy is designated as I, moderate complexity anatomy II, and high complexity as III. Patients with no significant residual lesions or sequelae are designated as A, mild residual lesions or sequelae are B, moderate residual lesions or sequelae are C, and severe residual lesions or sequelae are D. For example, a patient with a repaired secundum ASD and no pulmonary hypertension or patch leaks would be designated AP classification IA, whereas a patient with an unrepaired secundum ASD and severe pulmonary arterial hypertension would be designated AP classification ID. It should be noted that while this AP classification aims to determine severity relevant for clinical surveillance, management, and outcomes, transesophageal (and transthoracic) echocardiographic imaging protocols are mainly based on the underlying anatomical complexity.

Atrial and Ventricular Septal Defects

Echocardiography for patients with simple shunts such as patent foramen ovale (PFO), ASD, and ventricular septal defects (VSD) can be relatively straightforward. The goals of echocardiographic assessment include localizing the shunt and adjacent structures understanding the direction of the shunt and resultant pathophysiologic consequences and identifying or ruling out any additional associated CHD.

ASD is often diagnosed in adults, with the most frequent presenting symptoms being dyspnea on exertion, palpitations, and/or embolic stroke. There are four types of atrial level shunts: secundum ASD, primum ASD, superior or inferior sinus venosus defects, and unroofed coronary sinus. Secundum ASD is the most common atrial level shunts, followed by primum ASD, then sinus venosus defects, and lastly coronary sinus defects. As secundum ASD and sinus venosus defects are associated with partial anomalous pulmonary venous return, and TEE assessment should include identification of all pulmonary veins (Demos et al. 2004). Unroofed coronary sinus defects are associated with persistent left superior vena cava, and thus identification of one anomaly should prompt as assessment for the associated defect.

Multiple 2D and 3D views of the atrial septum are obtained to characterize the size of the defect, and color Doppler is used to assess the direction and degree of shunting and restrictive versus unrestrictive physiology based on spectral Doppler gradients. The TEE bicaval view is the most useful for the differentiation of secundum ASDs and sinus venosus defects. Atrial level

shunts lead to chronic right sided volume overload, with right atrial and right ventricular enlargement, right ventricular dysfunction, tricuspid regurgitation, and atrial arrhythmias. Pulmonary artery pressures are commonly elevated, but severe pulmonary arterial hypertension is uncommon in patients with atrial-level shunts.

Treatment includes either surgical patch repair or transcatheter device closure. Post-repair, patients remain at risk for tricuspid regurgitation, atrial arrhythmias, and RV dysfunction due to persistent chamber dilatation. Imaging adult patients after surgical or percutaneous ASD repair should focus on the identification of residual shunts or patch leaks, atrioventricular (AV) valve function from changes in structural architecture related to surgical patching or occluder devices, and signs of occluder device erosion.

Ventricular septal defects are among the most common congenital cardiac anomalies. Small VSD often close spontaneously in childhood, while large VSD typically require surgical closure early in life due to the development of heart failure symptoms from pulmonary over circulation. Adults with unrepaired small VSD are at risk for endocarditis due to the high-velocity turbulent jet impacting the tricuspid valve apparatus, and the development of endocarditis is a class IIb indication for VSD closure (Stout et al. 2019). Other indications for closure of a restrictive VSD are the development of double-chambered right ventricle, and progressive aortic regurgitation when associated with prolapse of the aortic valve leaflet into the left ventricular outflow tract (LVOT). Small-medium size muscular VSD and perimembranous VSD can often be closed using a transcatheter approach. Those with larger VSD, prior VSD patch repair with residual VSD due to patch dehiscence, endocarditis requiring surgical debridement, or concurrent valve repair, typically require a surgical approach.

Assessment of the adult patient with a VSD undergoing surgical repair or re-repair defines the location, size, and pathophysiologic sequelae of the intracardiac shunt. The surgeon should be made aware of vegetations and valve pathology in patients with endocarditis (Berglund et al. 2016). In severe cases, where there is a long-standing significant left to right shunt through the VSD, irreversible remodeling of the pulmonary endothelium occurs, resulting in severe pulmonary arterial hypertension and bidirectional shunting or shunt reversal, Eisenmenger syndrome. VSD closure is contraindicated in patients with Eisenmenger syndrome.

Infracristal VSD are best visualized with TEE in the 5 chamber mid-esophageal view, as well as the RV inflow-outflow view (between 6 and 9 o'clock), aortic valve long-axis view as well as deep transgastric 5 chamber view. Inlet VSD are best seen in the TEE views from mid-esophageal 4 chamber view and aortic valve long axis view. The mid-esophageal RV inflow-outflow view allows visualization of supracristal VSD, as well as the pulmonic valve.

Transcatheter VSD closure with occluder devices provides an attractive alternative to surgical closure. Complications after transcatheter VSD closure are uncommon, but may include device embolization, hemolysis or endocarditis due to residual shunting adjacent to the device, new valvular regurgitation due to valve trauma at the time of device placement, or heart block if the device impinges on the atrioventricular node. Thus, TEE examination of previously percutaneously or surgically repaired VSDs should include evaluation of the VSD repair, but also valvular function, and vegetations where clinically indicated.

Atrioventricular septal defects (AVSD), also known as AV canal defects or endocardial cushion defects, are a family of congenital defects located at the crux of the heart. Most patients with complete AVSD presented in childhood with heart failure from pulmonary overcirculation and have undergone repair. Patients presenting in adulthood with unrepaired AVSDs typically have a transition or partial AVSD and are symptomatic due to the left to right shunting across the nonrestrictive primum atrial septal defect. Perioperative TEE assessment of the patient with unrepaired partial or transitional AVSD should include careful evaluation of the inlet ventricular septum for a small VSD, evaluation of the left and right atrioventricular valves for regurgitation

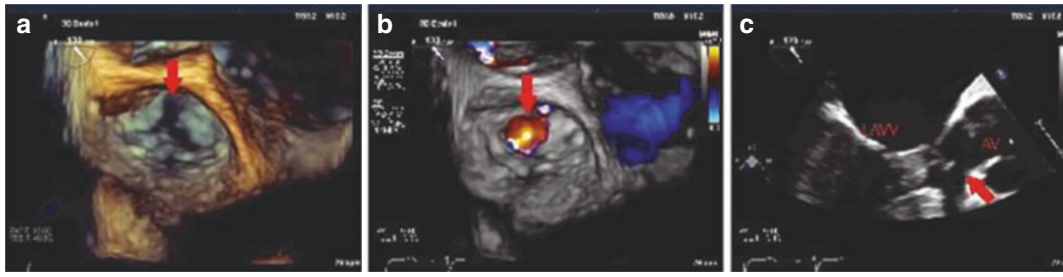

Fig. 1 22-year-old male with trisomy 21, previously repaired atrioventricular septal defect, presenting with endocarditis, severe left atrioventricular valve regurgitation due to a residual "cleft," and severe subaortic stenosis. The patient underwent left atrioventricular valve replacement and resection of the subaortic membrane. (**a**) 3-dimensional en-face view of the left atrioventricular valve and "cleft" (red arrow), (**b**) 3-dimensional en-face view of the left atrioventricular valve with color Doppler showing regurgitation originating at the "cleft" (red arrow), (**c**) mid-esophageal long axis view of the left atrioventricular valve, aortic valve and the subaortic membrane (red arrow). *AV* aortic valve, *LAVV* left atrioventricular valve

associated with a "cleft" requiring concurrent surgical repair. Adults with prior AVSD repair may require reoperation for atrioventricular valve stenosis or regurgitation, residual ASD or VSD, or left ventricular outflow obstruction, which are well assessed using standard perioperative TEE views (Fig. 1).

Tetralogy of Fallot

The vast majority of adults with Tetralogy of Fallot will have undergone an initial repair in childhood, involving closure of the VSD and relief of the RVOT obstruction (Sharkey and Sharma 2012). Associated cardiac and extracardiac anomalies include right aortic arch, coronary artery anomalies, hypoplastic pulmonary arteries, and DiGeorge syndrome (22q11 deletion) (Dabizzi et al. 1990). In recent decades, care of children born with TOF has favored earlier repair, typically within the first 6 months of life. Whenever feasible, a valve-sparing approach is now encouraged to minimize the need for reoperation for pulmonary regurgitation later in life. However, adult-aged patients at the time of this writing may have had their repair in an earlier era, when an RVOT incision and transannular patch were still widely used, with resultant severe pulmonary regurgitation. In both current and prior surgical eras, a right ventricle to pulmonary artery (RV-PA) conduit is utilized in patients with TOF with pulmonary atresia or those with anomalous coronary arteries that course anteriorly over the RVOT, precluding the necessary RVOT incision (Bove 2017). Adult patients with TOF and a RV-PA conduit may have conduit regurgitation and/or stenosis. Conduit stenosis may result from patient-prosthesis mismatch due to somatic growth after a pediatric-sized conduit was placed in childhood, and/or degenerative conduit stenosis. Approval of the 22 mm Medtronic Melody® transcatheter pulmonary valve in the US in 2010, and subsequent expansion of the use of 23, 26, and 29 mm Edwards Lifesciences Sapien® valves in the pulmonary position have significantly reduced reoperations for surgical pulmonary valve replacement in a large number of patients with TOF. For those adults with prior transannular patch repair and pulmonary valve annular dimensions that are too large for the Melody® and Sapien® transcatheter pulmonary valves, the development of hourglass shaped devices (Medtronic Harmony TPV®) designed to anchor in the RVOT and main pulmonary artery has provided additional options for a transcatheter approach in these patients (Fig. 2). Nonetheless, surgical pulmonary valve replacement remains indicated for those patients whose coronary artery anatomy are prohibitive for transcatheter pulmonary valves, those who require surgical pulmonary valve replacement for endocarditis, and those who also require other concurrent surgical interventions.

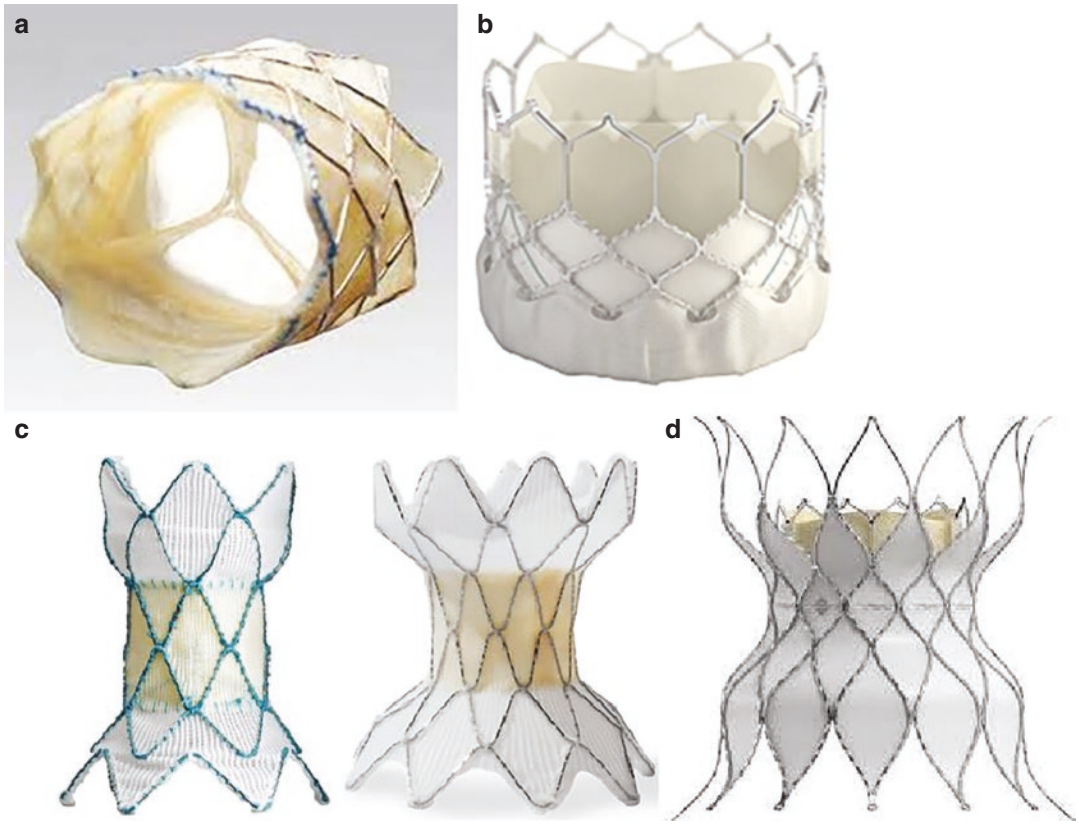

Fig. 2 Transcatheter pulmonary valves and right ventricular outflow tract reducers. (**a**) Medtronic Melody® transcatheter pulmonary valve, (**b**) Edwards LifeSciences Sapien S3 transcatheter valve, (**c**) Medtronic Harmony® TPV 22 (left) and 25 (right), (**d**) Edwards LifeSciences Alterra Adaptive Prestent

Intraoperative TEE for the adult patient with TOF with pulmonary valve regurgitation or RV-PA conduit stenosis/regurgitation undergoing reoperation should include evaluation for additional common sequelae, including residual shunts from VSD patch leaks, RV dilation, hypertrophy, and/or dysfunction and function from chronic progressive pulmonary regurgitation and/or valve/conduit stenosis, and functional tricuspid regurgitation from RV dilation. There is also potential for recurrent right ventricular outflow tract (RVOT) obstruction at the subvalvar or supravalvar areas, and thus corresponding views of the entire RV outflow tract including the infundibulum and main and branch pulmonary arteries are necessary. Imaging of RV-PA conduits by TEE may be challenging due to the anterior position and extensive calcium deposition; the upper esophageal and gastric views are often helpful. Assessment of the infundibulum and pulmonic valve or RV-PA conduit with TEE RV inflow-outflow views and in the mid-upper esophageal short axis view aids in the evaluation of stenosis along the RVOT and PA (Fig. 3). Furthermore, there should be interrogation of the main and branch pulmonary arteries for stenosis, which is accomplished with 2D and CFD with and without continuous wave Doppler in the ME Asc Ao SAX view. RV function should be evaluated by visualizing the ventricle in the ME 4Ch, ME RV inflow-outflow, TG SAX, DTG 5Ch views.

Dilation of the aortic root and ascending aorta to diameter ≥40 mm occurs in approximately 30% of adults with TOF and can be associated with aortic regurgitation (Mongeon et al. 2013). However, the incidence of aortic dissection in

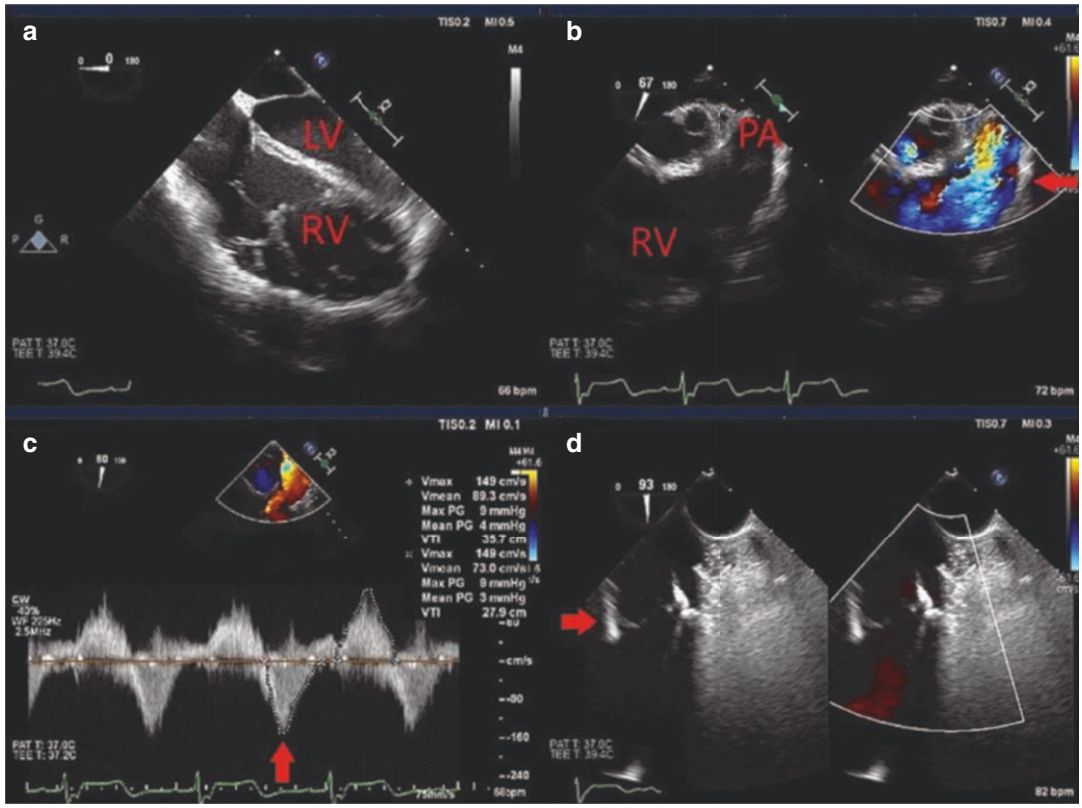

Fig. 3 30 year-old female with repaired tetralogy of Fallot and chronic severe pulmonary regurgitation, referred for surgical pulmonary valve replacement. (**a**) Midesophageal 4-chamber view demonstrating a severely dilated right ventricle with prominent trabeculations, and small, underfilled left ventricle, (**b**) midesophageal short-axis view showing no residual pulmonary valve tissue (left panel), and color Doppler showing severe pulmonary valve regurgitation (right panel), (**c**) spectral Doppler tracing from the midesophageal 4-chamber view showing no significant gradient across the RVOT, and a short spectral Doppler envelope in diastole (red arrow) which returns to baseline prior to systole, consistent with severe pulmonary valve regurgitation, (**d**) upper esophageal view after surgical pulmonary valve replacement demonstrating a well-seated bioprosthetic valve (red arrow, left panel) with no intravalvar or paravalvar regurgitation by color Doppler (right panel). *LV* left ventricle, *RV* right ventricle, *PA* pulmonary artery

patients with repair TOF is low (Egbe et al. 2019). The aortic root and ascending aorta should be evaluated in the ME AoV LAX view.

Left-Ventricular Outflow Tract Obstruction

Left ventricular outflow tract (LVOT) obstruction can occur at any level, from the left ventricle to the aorta. Subaortic stenosis, congenital aortic valve stenosis, supravalvar aortic stenosis, and aortic coarctation are the most common causes of LVOT obstruction (LVOTO).

Subaortic stenosis may be due to a discrete subaortic membrane (Fig. 4) or tunnel-like stenosis. Indications for surgery include symptomatic severe subaortic stenosis, ventricular dysfunction, and progressive aortic regurgitation due to damage to the aortic valve leaflets from the turbulent jet. Subaortic stenosis may recur after the initial surgery. In one series, the recurrent rate for discrete subaortic membrane was 14.7%, whereas the risk of recurrence in tunnel-type subaortic stenosis was significantly higher at 71% (Brauner et al. 1997). While subaortic membrane resection is usually adequate in those with discrete membranes, LVOT reconstruction with an anterior

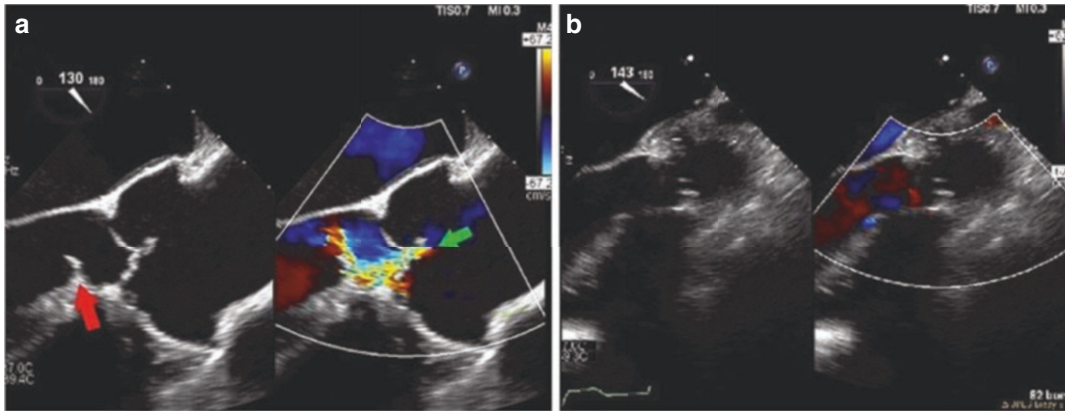

Fig. 4 A 40-year-old woman with a discrete subaortic membrane. (**a**) Baseline intraoperative midesophageal long axis view showing the discrete subaortic membrane (red arrow, left panel), with associated aortic regurgitation (green arrow, right panel). (**b**) Post-surgical intraoperative midesophageal long axis view showing no residual subaortic membrane (left panel), and a repaired aortic valve without regurgitation (right panel)

aortoventriculoplasty (Konno-Rastan procedure) may be required to adequately relieve tunnel-type LVOT stenosis. In the presence of postoperative gradient of >10 mmHg was associated with a higher risk of recurrence. Concurrent aortic valve repair or replacement may be required in patients with aortic regurgitation. Intraoperative TEE should therefore include careful assessment for residual LVOT stenosis, as well as evaluation for aortic valve stenosis and regurgitation postintervention. If a Konno-Rastan procedure is performed, the ventricular septum should be interrogated to ensure there is no residual iatrogenic ventricular level shunt.

Bicuspid aortic valves are the second most common congenital heart defect and are the most common cause of valvular aortic stenosis in the congenital population. While neonates, children, and young adults with congenital aortic stenosis often benefit from transcatheter balloon valvuloplasty, once the valve becomes more calcified in adulthood, the degree of improvement of aortic stenosis decreases, and the risk of residual aortic regurgitation and stroke increases. Thus, in most adult patients with congenital aortic stenosis, surgical intervention is recommended (Stout et al. 2019). In addition, dilation of the aorta is common in adults with bicuspid aortic valve and increases with age, with a prevalence of 56,%, 74%, 85%, 91%, and 88% at the age quintiles of younger than 30 years, 30–39 years, 40–49 years, 50–60 years, and older than 60 years, and aortic dilation may prompt surgical referral and concurrent aortic valve intervention, even in patients who may not meet yet criteria for aortic valve intervention due to aortic stenosis or regurgitation (Della Corte et al. 2007). In patients with congenital aortic stenosis as part of Shone complex, the left atrium and mitral valve apparatus should be inspected for evidence of supramitral membrane or ring using 2D imaging as well as ventricular inflow stenosis with spectral Doppler (Shone et al. 1963).

Although bioprosthetic or mechanical aortic valve replacement remains the most frequently performed intervention for adults with congenital aortic valve stenosis, many congenital heart surgery programs also offer alternative approaches such as the Ross procedure and/or aortic valve reconstruction (Ozaki procedure). In the Ross procedure, the patient's own pulmonary valve and root are autografted into the aortic position with reimplantation of the coronary arteries, and a graft is placed in the RV-PA position. In a retrospective study, patients who underwent the Ross procedure had comparable short-term mortality and lower long-term mortality compared with those who underwent bioprosthetic or mechanical valve replacement, though with the rate of reoperation compared with those who underwent

mechanical valve replacement (El-Hamamsy et al. 2022). Aortic valve repair techniques may be used in patients with aortic regurgitation. Postintervention intraoperative TEE should focus on identifying residual aortic regurgitation that may be eccentric, paravalvar regurgitation for valve replacements, and coronary artery ostia for patients who have undergone coronary reimplantation (i.e., Ross or Bentall procedures).

Supravalvular stenosis is typically associated with Williams-Buren syndrome, which is caused by a mutation in the elastin gene and results in an elastin arteriopathy. Supravalvar aortic stenosis typically involves the sinotubular junction, but can also include narrowing of the proximal tubular ascending aorta. The supravalvar aortic stenosis may affect the coronary artery ostia, causing stenosis. Cardiovascular collapse and death with induction of anesthesia have been reported in patients with Williams syndrome, and have been attributed to coronary ischemic due to coronary ostial stenosis and the sudden decrease in afterload with anesthesia.

Intraoperatively, evaluation of the patient with left ventricular outflow tract obstruction should include 2D imaging with color and spectral Doppler as well as 3D imaging when feasible to assess the level of obstruction, gradients, and flow dynamics. Color flow Doppler is particularly useful when attempting to determine the specific level of stenosis, using the ME AoV LAX, ME LAX, TG LAX, and DTG 5Ch views (TEE). For the reasons delineated above, baseline and postintervention of assessment of the LVOT, aortic valve, aortic root and ascending aorta, and coronary arteries are essential in the patient undergoing surgery for LVOTO.

D-Transposition of the Great Arteries

In the D-transposition of the great arteries, the pulmonary artery and aorta are transposed, so that the aorta arises anteriorly from the right ventricle, and the pulmonary artery arises posteriorly from the left ventricle. Adults born with d-TGA in the earlier surgical will likely have undergone an atrial switch procedure (i.e., Senning or Mustard), with baffles redirecting the IVC and SVC to the subpulmonary left ventricle, and the pulmonary veins to the systemic right ventricle. As the sequelae of D-TGA after the atrial switch include baffle stenoses, baffle leaks, systemic RV dysfunction, and tricuspid regurgitation, indications for reoperative in the adult with D-TGA after the atrial switch may include baffle revision or tricuspid valve replacement.

Intraoperatively, the atrial baffles after either a Mustard or Senning should be assessed for commonly present baffle leaks or baffle stenosis. The optimal views for the atrial baffles are the ME 4Ch and ME bicaval windows, and TG views of cavoatrial connection. TEE has superior sensitivity and specificity to detect baffle leaks when 2D imaging is used in combination with agitated saline, with injections from lower extremity IVs to evaluate for IVC baffle leaks, and injections from upper extremity IVs to evaluate for SVC baffle leaks. Bi-plane and multi-planar imaging helps to localize baffle leaks, and addition of CFD reveals the direction of shunting. Turbulent flow using CFD and baffle flow with velocities greater than 1.6 m/s on SD are indicative of baffle stenosis.

Most patients born with D-TGA in the late 1980s or early 1990s and later will have undergone the arterial switch operation (Jatene), in which the aorta and pulmonary artery are transected above the root and transposed, so that the pulmonary artery arises anteriorly from the right ventricle, and the aorta arises posteriorly from the left ventricle. The coronary arteries are then excised and reimplanted in the neoaortic root. Reoperation for patients with D-TGA and prior arterial switch is typically for neoaortic root dilation and/or neoaortic valve regurgitation. Surgical intervention may therefore entail a valve-sparing root replacement, an aortic valve replacement, or a Bentall procedure. The reimplanted coronary arteries should be carefully assessed both pre- and postintervention. The anterior pulmonary artery should be evaluated from the upper esophageal view for supravalvar

pulmonary artery stenosis, which may occur due to the anterior repositioning of the pulmonary artery.

In patients with D-TGA and left ventricular outflow tract obstruction are likely to have undergone either a Rastelli, Nikaidoh, Réparation à l'Etage Ventriculaire (REV) or En-Bloc Rotation operation. Given the anterior positioning of the RV-PA conduit after Rastelli repair for TGA with LVOT obstruction, echocardiographic examination of the proximal and distal conduit often requires nonstandard views which can include variations of the ME RV inflow-outflow view, and ME Asc Ao SAX view. Additionally, both Rastelli and arterial switch repairs require a review of all outflow tracts for the presence of obstruction and evaluation of any surgically placed VSD patch or baffle for residual shunt.

Congenitally Corrected Transposition of the Great Arteries

Patients with congenitally corrected transposition of the great arteries (cc-TGA) have atrioventricular discordance and ventriculoarterial discordance, so that the right atrium drains to the morphologic left ventricle, which ejects blood forward to the pulmonary artery. The left atrium receives pulmonary venous return, and drains to the morphologic right ventricle, which ejects blood forward to the aorta (Graham et al. 2000). Adults with cc-TGA most commonly require operation for tricuspid regurgitation, which may be due to Ebsteinoid malformation of the tricuspid valve, or may be secondary to dilation of the systemic right ventricle. Use ME 4Ch and ME Asc Ao SAX views (TEE) help to orient the echocardiographer with respect to relationships of the ventricles and great vessels to each other. As in D-TGA after atrial repair, specific attention needs to be paid to the functional differences between a systemic subaortic right ventricle and a normally functioning subpulmonic right ventricle during the echocardiographic assessment. Additional careful inspection of the atrial and ventricular septa as well as the tricuspid valve is warranted.

Ebstein Anomaly

Ebstein anomaly can occur in conjunction with other CHD such as ccTGA or in isolation. In the Ebstein anomaly, there is an apical displacement of the septal and posterior tricuspid leaflets, and elongation of the anterior leaflet (Yuan 2017). Due to the apical displacement of the tricuspid leaflet, the basal portion of the right ventricle is "atrialized" and the functional right atrium is enlarged. The malformed tricuspid valve in Ebstein anomaly may have varying degrees of regurgitation. Ebstein may be associated with interatrial communications (PFOs, ASDs), VSDs, pulmonary atresia, accessory conduction pathways (Wolf-Parkinson-White), and left-sided pathology including mitral valve prolapse and LV noncompaction. TEE examination of Ebstein anomaly should delineate the structure and function of the Ebstein tricuspid valve. The ME 4Ch view with focus on the RV, ME RV inflow-outflow view, as well as the TG RV basal SAX and TG RV inflow views enables a comprehensive assessment of the Ebstein valve (Morray 2016). Color flow Doppler and spectral Doppler are utilized to assess the presence of RV inflow regurgitation, intracardiac shunts, and RV outflow stenosis. The surgical technique for repair depends upon the age at time of intervention as well as the underlying pathology. The Cone reconstruction is an excellent surgical option in pediatric and adult patients that require intervention (Fig. 5). Alternatively, for regurgitation of an Ebstein tricuspid valve not amenable to repair, or an Ebstein valve that has been previously repaired, tricuspid valve replacement may be performed. Postoperatively, echocardiographic assessment of a repaired tricuspid valve is important, as valves with moderate or greater residual regurgitation may require replacement in the same surgery. As patients with Ebstein anomaly also commonly suffer from RV dysfunction, assessment of the RV function pre- and postcardiopulmonary bypass will guide inotropic therapy in the early postoperative period. Pre- and postrepair Ebstein's patients may also present to the catheterization laboratory for electrophysiology studies, ablation procedures, and for placement of pacemakers.

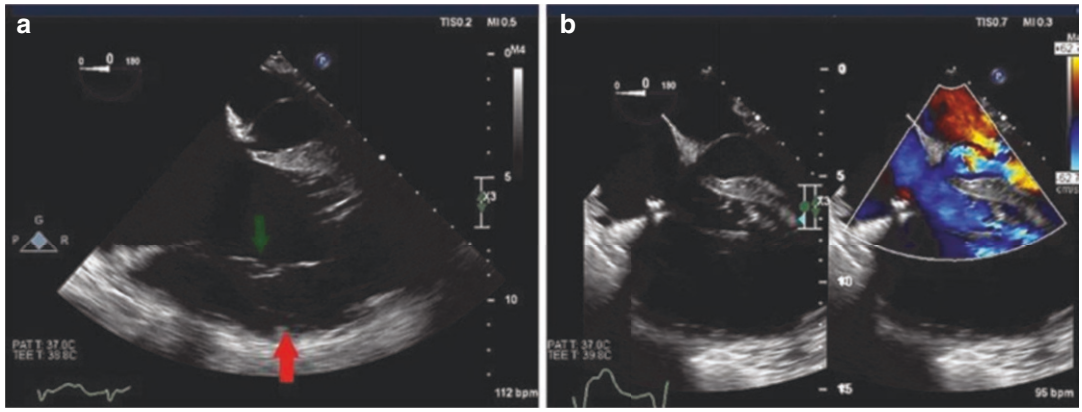

Fig. 5 A 32-year-old man with unrepaired Ebstein anomaly referred for tricuspid valve repair. (**a**) Intraoperative baseline imaging, midesophageal 4-chamber view focusing on the tricuspid valve. Note the elongated anterior leaflet (green arrow) and attachment of the anterior leaflet to the right ventricular free wall (red arrow). (**b**) After Cone repair of the tricuspid valve, the anterior leaflet of the tricuspid valve has been mobilized for tricuspid valve reconstruction, and color Doppler demonstrates the new functional orifice of the tricuspid valve without color flow acceleration to suggest stenosis

Single Ventricle

Single ventricle palliation, the Fontan procedure, is the surgical pathway for ACHD patients with congenital heart defects, which preclude the possibility of biventricular repair, such as hypoplastic left heart syndrome, mitral atresia, tricuspid atresia, pulmonic atresia, double inlet or outlet right ventricle, unbalanced complete AVSD, and others. In the Fontan procedure, systemic venous return is directed to the pulmonary artery without an intervening ventricular pump, and there is a functional single ventricle that pumps pulmonary venous return to the aorta. Given the multitude of intracardiac anomalies that can lead to surgical palliation, the echocardiographic exam on these ACHD patients should include systemic ventricular size and function, systemic atrioventricular and semilunar valve morphology and function, systemic outflow tract flow dynamics, and cavopulmonary anastomotic dimensions and flow, in addition to aorta characteristics. Three major surgical techniques have been employed to such a circulation: the atriopulmonary connection, the lateral tunnel Fontan, and the extracardiac Fontan.

Adults with patients with Fontan palliation most commonly require reoperation for atrioventricular valve regurgitation, ventricular outflow tract obstruction. Those with atriopulmonary Fontans may require revision to a lateral tunnel or extracardiac Fontan for indications of recurrent atrial arrhythmias or thrombotic complications. When intraoperative echocardiographic imaging is performed, midesophageal views via TEE can assist in the Fontan evaluation (Hauser et al. 2017). The Fontan pathway should be assessed for thrombus, stenosis, or fenestrations/leaks with color Doppler and spectral Doppler. Measurements independent of geometric constraints, such as tissue Doppler imaging and strain, can be useful in assessment of ventricular function.

Conclusion

Significant advances in the treatment of congenital heart disease patients has led to a decrease of mortality in this patient population and surviving adults comprise most of the patients with CHD (Marelli et al. 2007). Standardization of

transthoracic and transesophageal echocardiography offers important advantages when managing adults with congenital heart disease. Aside from establishing baseline studies for long-term surveillance and research utilization, uniform echocardiography in the perioperative setting can facilitate the performance and interpretation of frequent follow-up imaging and simplify interpretation for clinicians less familiar with CHD physiology. While certain pathophysiologic changes are common to ACHD and are easily visualized by standard echocardiography, knowledge of the key features specific to individual CHD lesions and their optimal image acquisition are important skills every perioperative clinician performing echocardiography on patients with congenital heart disease should be familiar with.

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Pediatric Cardiovascular Monitoring

Christopher Denny and David F. Vener

Abstract

Continuous monitoring during anesthesia gives the practitioner information on physiologic changes that may require an intervention. The monitors do not make these interventions, and interpretation and action of the practitioner are still required to affect outcome and minimize adverse events. The focus of this chapter is to discuss both the noninvasive and invasive cardiac monitors that are used in cardiac surgery, risks in their placement, and the information that can be obtained from them.

Keywords

Pulmonary artery catheter · Arterial line · Ventricular assist device · Central venous line Pulse contour analysis

A 16-year-old male requires emergent ventricular assist device (VAD) placement for dilated cardiomyopathy. The patient has two peripheral intravenous lines and no invasive monitoring upon arrival to the operating room. The patient is transferred from the stretcher to the bed. The noninvasive monitors are removed and replaced by those on the operating room table. The blood pressure is 82/45 with a HR of 126; the pulse oximetry is showing low signal quality, and no value is on the monitor. The patient is on inotropic support of epinephrine 0.02 mcg/kg/min and milrinone of 0.5 mcg/kg/min and is breathing spontaneously with supplemental oxygen at 2 l/min via nasal cannula.

Noninvasive Monitoring

The initial monitors are placed on the patient in the pre-induction period in cooperative patients. For younger, noncooperative patients it is sometimes necessary to proceed with minimal monitoring until the patient is sufficiently anesthetized to allow them to be placed. These monitors are a standard of care for all anesthetics but are particularly important in adult and pediatric cardiac patients due to their increased risk of cardiac arrest (Morray et al. 2000; Nashef et al. 2002). The standard monitors include a pulse oximeter, a 5-lead continuous electrocardiogram (ECG) leads, a noninvasive blood pressure, end-tidal CO_2, and a temperature probe (American Society of Anesthesiology 2020).

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Pulse Oximetry

Pulse oximetry was invented in the early 1970s, but it was not until the early 1980s that there was widespread adoption in the operating room (Severinghaus and Honda 1987). Pulse oximetry takes advantage of the fact that both oxy- and deoxyhemoglobin are chromophores, which are molecules that absorb and reflect certain wavelengths of light. The pulse oximetry probes transmit both red and infrared light to the pulsatile component of blood supply across a vascular bed. The wavelengths that pass through are measured, and the oxygenation saturation is calculated continuously by measuring and comparing pulsatility changes during the systolic and diastolic components of the pressure wave.

The use of the pulse oximeter can be complicated in some cardiac or perfusion abnormalities as it is dependent on pulsatility and can be altered by profound hypoxia, hypoperfusion, peripheral vasoconstriction, and other factors. Therefore, the pulse oximeter can be inaccurate due to poor flow to extremities in shock states or peripheral vasoconstriction due to the use of potent vasoconstrictors and hypothermia. This can also be a concern in patients who have a continuous flow VAD or are placed on extracorporeal membrane oxygenation (ECMO) due to the lack of pulsatility with these devices (Trivedi et al. 1997a, b). The placement of the probe in a central location such as across the bridge of the nose or on an earlobe may improve accuracy in these low-flow states as blood flow to the cerebral circulation is preferentially preserved. There is no way of improving the accuracy during profound hypoxia though the most common concern is an underestimation of oxygen saturation (Severinghaus et al. 1989). Care must be taken when placing pulse oximeter probes on distal extremities in patients with low-flow states to avoid ischemic injury to the underlying skin and tissues.

5-Lead Electrocardiogram

There are two types of ECG most commonly used in anesthesia: 3- and 5-lead The purpose of the ECG is to help the anesthesia provider define the rhythm and to monitor for heart strain or ischemia. The 5-lead ECG is most commonly used in the cardiac operating room as it provides information regarding the anterior, lateral, and inferior portions of the heart and can generally be placed without affecting the surgical field. The 12-lead ECG is rarely used in the operating room environment as the lead placement would lie within the surgical field, but is most commonly utilized in the ICU intermittently as it gives more detailed information about potential arrhythmias or ischemia. ECG interpretation is covered in chapter "Electrocardiography: Basic Knowledge with Focus on Fetal and Pediatric ECG.

Blood Pressure

Automated noninvasive automated blood pressure monitoring (NIBP) has been used in the operating room for over 40 years. The most common monitoring system uses the oscillometric method via a size- and age-appropriate cuff (Frohlich 1988). The oscillometric method initially has the cuff achieve a pressure above the systolic pressure of the patient. The cuff pressure gradually decreases and the artery will expand and contract secondary to pulsatile blood flow and the resultant pressure change in the cuff is sensed by the monitor. The peak amplitude of the expansion and contraction is approximately the mean arterial pressure (MAP) (Graettinger et al. 1988). Individual companies have proprietary algorithms to compute systolic, mean, and diastolic pressures.

Noninvasive blood pressure monitoring is reasonably accurate and usually within 5% of intra-arterial monitoring in a hemodynamically stable

patient but can be significantly less reliable in unstable patients, those on continuous flow devices such as an LVAD or those on high doses of vasoactive agents. Despite the accuracy, the algorithms that compute the pressures are fallible with extremes in pulse pressure, heart rate, and arterial stiffness (O'Brien et al. 2001; van Montfrans 2001). The blood pressure cuffs must also be placed at the correct locations and be sized appropriately. The cuff should cover approximately 80% of the circumference of the upper arm and two-thirds the distance from the elbow to the shoulder. The placement of the cuff in the lower extremity is commonly done but may lead to inaccuracy in the reading. Altering the position of the arm such as having them up alongside the head, as is common in the cardiac catheterization lab, can lead to significant discrepancies between intra-arterial and NIBP readings.

Near-Infrared Spectroscopy Monitors

Near-infrared spectroscopy (NIRS) monitors are routinely used at most cardiac surgery centers today, both in pediatric and adult patients. They can be both a neurologic and a cardiac monitor as the NIRS can be considered a surrogate for the mixed venous saturation of the brain. A full discussion on this topic can be found in chapter "Central Nervous System Monitoring in Pediatric Cardiac Surgery" Neurologic Monitoring. When at all possible it is very helpful to place these probes prior to oxygenation and induction of anesthesia in order to determine an accurate baseline reading.

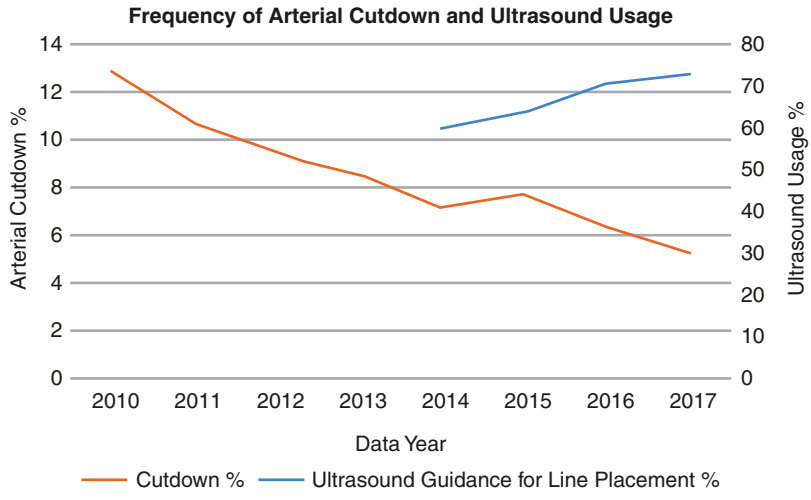
The pulse oximeter probe is adjusted and placed on the ear and the signal strength improves and the reading is 99% on facemask oxygen supplementation. Induction is completed with etomidate, fentanyl, and rocuronium, and vital signs remain stable with intubation and the transition to positive pressure ventilation. Arterial line placement is successful with ultrasound guidance in the right radial artery. The arterial line waveform is dampened and there is poor blood return. The arterial line was placed on the first attempt.

Invasive Monitoring

The weak peripheral pulse oximetry signal and the poor blood return on the peripheral radial arterial line are likely due to compromised peripheral blood flow. A femoral arterial line is subsequently placed with an improved waveform and much-improved blood return. The waveform still has a very rounded upstroke concerning for poor cardiac output. The BP reading on the radial line is 66/54 while on the femoral line is 95/43.

Arterial Line

Arterial line access is routinely obtained in cardiac surgery for beat-to-beat pressure monitoring, for monitoring pressure on cardiopulmonary bypass (CPB), and for obtaining blood for laboratory analysis from the patient. Percutaneous access by ultrasound or palpation is often the first choice technique particularly in neonates, but a surgical cutdown may be necessary at times. A recent review of the Congenital Cardiac Anesthesia Society's database showed that the incidence of arterial cutdowns in the United States has been decreasing as the availability and usage of ultrasound guidance has become commonplace (Vener et al. 2020). The most common location for arterial access is the radial artery, but the ulnar, axillary, brachial, and femoral arteries and the umbilical artery (in newborns) may also be considered.



From: Vener et al

The most concerning complication from arterial access is distal ischemia. Most anesthesiologists prefer cannulating vessels with significant collateral circulation. The brachial artery is often thought of as having less collateral flow and is only used as an option of last resort in children but is more commonly utilized in adults. The radial artery has ulnar circulation to the hand, and the Allen's test is often used to reconfirm collateral flow though studies have questioned its need and efficacy in routine use (Slogoff et al. 1983; Bertrand et al. 2014). The ulnar artery has historically been avoided as it was thought to be the major source of blood flow to the hand, however Haerle et al. (1963) showed using Doppler sonography, the ulnar rarely dominates at the level of the forearm after giving off collateral branches. Its use in congenital cardiac anesthesia has increased dramatically with the advent of ultrasound use in the operating room as this allows better visualization of the deeper vessel and confirmation of radial and ulnar patency. Pseudoaneurysms are another rare complication of arterial cannulation occurring at a rate of 0.09–0.3% depending on the location of cannulation (femoral being the highest risk). Local and systemic infection is also uncommon, less than 1% regardless of location in a review from Scheer et al. (2002).

The umbilical artery is the optimal site for neonatal arterial lines in the perinatal period. It is relatively easy to place catheters in the umbilical artery under direct visualization in the newborn, and they have low complication rates. Appropriate positioning needs to be confirmed by radiography after placement. Peripherally placed arterial catheters in children and, specifically, neonates are associated with increased risks, and temporary ischemia was reported to be over 4% in one study by Hack et al. (1990). It is important to closely monitor the extremity in which the catheter is placed during and after surgery and it is our practice to maintain a pulse oximeter on the distal extremity beyond the catheter. Catheter choice can be difficult, especially in neonates. 24 g catheters are frequently used in patients under 5 kg, but they are unreliable and easily kinked and may not last for the entire perioperative period. 22 g catheters are commonly used in patients up to 20–30 kg patients and 20 g catheters are used for larger patients. Some practitioners advise rewiring to specific arterial line catheters, 2.5 Fr for neonates and infants and 3 Fr for larger patients. These catheters have the advantage of being stiffer and more easily sutured in place.

There are special considerations that should be taken into account with arterial line placement and interpretation. The femoral artery may be preferred in cases of poor distal perfusion. Radial arterial cannulation may be difficult in neonates, and its accu-

racy can come under question because of changes in vascular tone and intravascular volume when coming off bypass. Dampening and resonance can affect arterial line transmission. Dampening usually occurs when the energy given by the pulse is lost in the transduction system. This can occur when the line is kinked, if it has an air bubble or clot inside it, or if there are any loose connections. Resonance occurs when the oscillatory frequency of the system is the same as that of the arterial waveform. This can be improved by using a stiffer connector or a shorter and wider transduction system. Dampening and resonance are less likely to occur in femoral arterial lines than in radial arterial lines.

An accurate waveform can give a significant amount of information to the cardiac rhythm and function of the heart. The area under the systolic portion of the curve is proportional to the stroke volume (Bourgeois et al. 1976). Some studies have stated that cardiac output (CO) can be estimated using the waveform and a rounded upstroke could be a sign of worsening function (Tartiere et al. 2007). The location of the catheter will also impact the waveform due to increasing wave reflection in distal smaller arteries (O'Rourke 1990). The peak of the systolic wave will be higher and there will also be a lower diastolic pressure.

Overall, arterial cannulation can be done safely and is an excellent source of hemodynamic and laboratory monitoring. Patient age and perfusion status should be considered when discussing the location for placement, and distal perfusion should be closely monitored if there are any concerns. It is also important to consider whether the patient has anomalies in vascular anatomy such as an aberrant subclavian artery as this may affect monitoring when placing a transesophageal echocardiography probe.

Central Venous Lines

The patient is 16 years old, 164 cm tall and also weighs 74 kg. The decision is made to attempt a central venous line in the right internal jugular vein. The line is placed utilizing ultrasound guidance with the Seldinger technique while the patient is maintained in a flat position to avoid excess venous return and worsening of the heart failure. There was an ectopy with the placement of the wire that improves after pulling the wire back two centimeters. A 7 Fr 15 cm triple lumen line is then placed over the wire with good blood return in all lumens.

Percutaneous central venous lines are placed in most patients undergoing cardiac surgery. The most common reasons are central venous pressure (CVP) monitoring, medication administration, and difficult peripheral access. The placement of these lines is generally safe, especially in well-trained hands. These lines often have multiple lumens to be able to monitor CVP and simultaneously administer medications or draw blood (Fig. 1).

There are three large veins used for central line placement, internal jugular (IJV), subclavian (SCV), and femoral (FV). All three locations have benefits and risks. The FV is thought of as the easiest to cannulate and the least likely to cause major injury with initial line placement. However, femoral line placement has a higher infection risk in adult patients, though the data are not as clear in pediatrics (O'Grady et al. 2011). The IJV has a slightly higher complication rate than FV cannulation with carotid cannulation/injury and pneumothorax being the most concerning. The SCV has the highest complication rate due to arterial injury and pneumothorax, but also has the lowest infection rate of the three (Kornbau et al. 2015), and is thought to be the most comfortable for the patient postoperatively. Additionally, the SCV catheter may become occluded during the operative procedure when sternal retraction is utilized and the catheter is "pinched" between the clavicle and the first rib.

Routine use of ultrasound has become common and is the standard of care for placement in the IJV according to the ASA guidelines and a recent study by Reusz and Csomos (2015). Multiple studies have shown a decrease in the complication rate when ultrasound is used though it does take some training to become facile (Hind et al. 2003). Appropriate line length can be difficult to estimate for pediatric patients. Two studies have come up with specific formulas based on the height in cm for right internal jugular vein catheter placement (Andropoulos et al. 2001; Yoon et al. 2006) (Table 1).

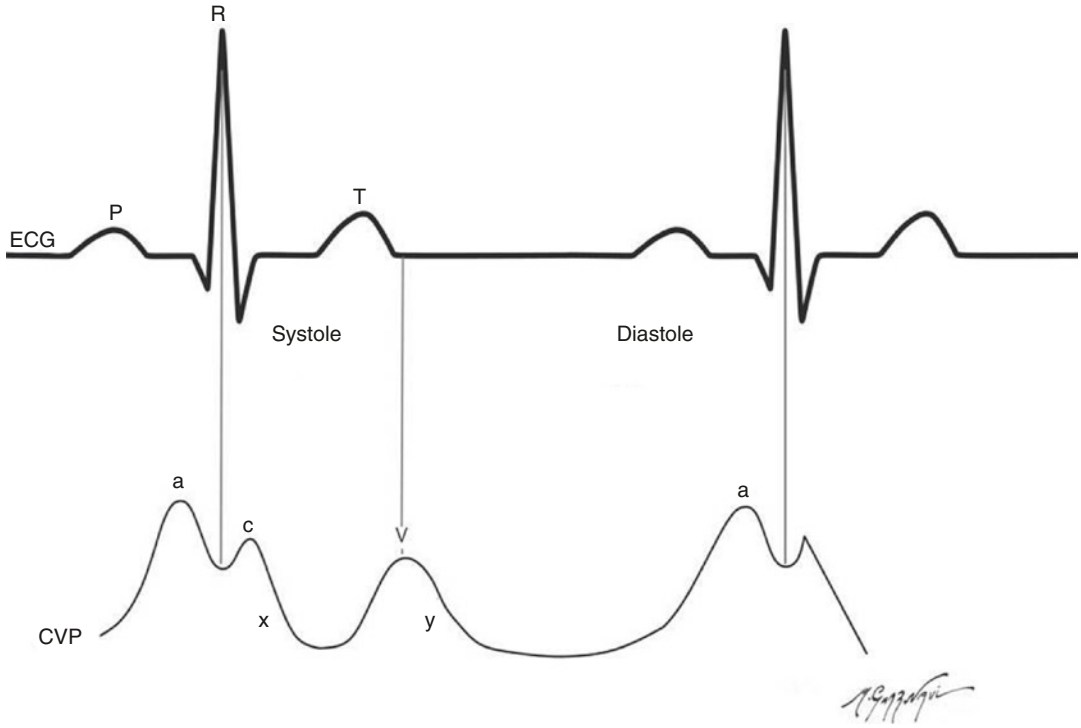


Fig. 1 CVP waves and the relation with ECG (Modified from Dabbagh (2014). Published with kind permission of © Springer, 2014. All Rights Reserved)

Table 1 Two alternative formulas for calculating length of catheter placement via the right internal jugular vein approach (Andropoulos et al. 2001; Yoon et al. 2006)

1. Andropoulos et al. 2001	2. Yoon et al. 2006
(Ht/10-1) cm if Ht < 100 cm	(0.07 × Ht) + 1.7
(Ht/10-2) cm if Ht > 100 cm	

For example, an 80 cm patient should have a 7 cm line placed per formula 1 in the right internal jugular vein and a 7 cm line placed per formula 2. Our patient who is 164 cm should have a 14 cm line placed per formula 1 while a 13 cm line placed per formula 2. While not perfect, these estimates can give a practitioner a general sense of the optimal length of the line. Line placement should be confirmed at the earliest possible time by chest radiography. Optimal position is generally felt to be with the tip of the catheter located at the SVC—right atrial junction for IJ and SCV lines and at the IVC—right atrial junction for FV lines. It is very important to consider the tip placement in patients with a patent atrial septum as it is quite possible to advance the catheter into the left atrium, resulting in possible systemic embolization of air during the flushing of the line.

Long-term complications from CVL placement may include infection, clot formation, and vessel stenosis or obstruction—particularly in patients with poor cardiac output and blood flow and the infusion of more sclerotic agents such as calcium chloride. Placement should be completed under sterile conditions and following appropriate CVL bundle guidelines, including chlorhexidine skin preparation, full gown and gloves for the provider, and whole body draping for the patient.

At some pediatric cardiac centers, it is the practice for the surgeons to place either right or left atrial lines directly into the atria at the conclusion of the intracardiac repair immediately prior to separating from bypass rather than utilizing percutaneously placed lines. Left atrial lines in particular may be helpful in trending left ventricular dysfunction as well as volume status. Surgically placed lines are then tunneled out through the skin

Table 2 Common CVP changes in tracing in different cardiac conditions

Cardiac condition	Change in CVP tracing
Atrial fibrillation	Loss of A wave
A-V dyssynchrony/A-V block	Cannon A waves
Tricuspid regurgitation	Large V wave
Cardiac tamponade	Loss of Y descent

and connected to pressure monitoring transducers and vasoactive agents are connected as well. These lines have their own set of complications, including inadvertent migration either deeper into the heart or displacement out of the atria. Most significantly, they have the risk of tamponade after removal if the "stay" suture around the catheter does not adequately seal off the entry point into the atrium. It is the practice at our institution to have a surgical team available in the hospital during the removal of these lines due to the rare incidence of tamponade and any hint of hemodynamic instability after removal warrants immediate echocardiography to rule out this complication.

CVP is the primary hemodynamic measure that is obtained by the placement of a central venous line. The pressure reading gives information regarding the venous system as a whole. The waveform is created by the transmission of energy during events through the cardiac cycle. There are many variables that affect the waveform leading to a number of different manifestations. A few abnormalities are common, and their effects on the waveform should be known. Dampening and resonance are rarely a problem with CVP monitoring since it is a low-pressure system. However, the line is also more likely to be located against a vessel wall for that same reason. In this case, the CVP monitoring will not be accurate, and the line position may need to be adjusted (Table 2).

Pulmonary Artery Catheter

The cardiac surgeon states that he would like a pulmonary artery catheter (PAC) instead of the central venous line. He would like to know the pulmonary artery pressure and monitor it during the placement of the VAD and in the immediate postoperative period to ensure that the left atrium is being adequately decompressed. A wire is placed in sterile fashion through the most distal lumen of the CVL. The CVL is then removed and the PAC is placed via *a sheath introducer and the catheter is attempted to be floated in the pulmonary artery. Because of both poor cardiac output and a distended failing heart the PA catheter does not advance readily into the main pulmonary artery and repeatedly coils in the right ventricle. The patient develops ectopy and subsequently ventricular tachycardia that does not improve with removal of the catheter from the ventricle. The patient is immediately cardioverted and no further attempts are made to float the Swan–Ganz at this time.*

Pulmonary artery catheters (PAC) have been used in cardiac surgery for measuring cardiac output (CO), mixed venous saturation, direct pulmonary artery pressures, and pulmonary capillary wedge pressure. They were routinely used until a number of studies including a Cochrane review and the ESCAPE trial questioned their effectiveness in the ICU and in the operating room (Pulmonary Artery Catheter Consensus conference: consensus statement 1997; Binanay et al. 2005; Rajaram et al. 2013). These studies, among many others, have resulted in a marked reduction in the number of PACs placed, though many institutions still place them routinely (Marik 2013b). The placement of a PAC in children is very uncommon and is often complicated by sheath size and intracardiac shunting that make the readings unreliable or inaccurate. Though now almost 20 years old, the Pulmonary Artery Consensus Conference recommended the use of PA catheters in children suffering from shock refractory to fluids and vasopressors, pulmonary hypertension, and acute lung injury when attempting to decipher cardiogenic from noncardiogenic causes. A recent review supported this statement and discussed the lack of evidence for their use (Perkin and Anas 2011). There is much more variability in adult patients, but a major meta-analysis looked at 13 randomized studies in cardiac ICU and surgical settings, which showed no significant improvement in any major outcome associated with PAC usage (Shah et al. 2005). In a recent study, the benefits of PACs were discussed in very specific cases including acute heart failure requiring inotropes (Sotomi

et al. 2014). Many experts also believe that there are patient-specific situations where the placement of a PAC may help management where no guidelines are in place (Kahwash et al. 2011).

When placed, a PAC can give information that cannot be accurately obtained from any other monitor system. CO monitoring can be completed via two means, thermodilution and oxygen consumption. Thermodilution is usually favored in adult patients due to its ease and the immediate value obtained without practitioner calculation. In this method, a known volume at a known temperature is injected into the patient via the catheter itself. The thermistor then reads the temperature downstream, and the CO is calculated, dependent on the temperature change and using the patient's body surface area (Ganz and Swan 1972). The thermistor placed on the catheter requires a larger sheath and, therefore, is often difficult to place in children and infants. Thermodilution is also not accurate when there is intracardiac shunting as seen in many congenital heart patients (Freed and Keane 1978). The Fick method of oxygen saturation sampling is instead routinely used. The Fick method requires the sampling of oxygen saturation at the pulmonary artery (venous oxygenation) and pulmonary vein (arterial oxygenation) with an estimated oxygen consumption based on the size of the patient to calculate CO (Rutledge et al. 2010). The peripheral artery oxygenation is often used as a surrogate for the pulmonary vein, but this assumes no significant intracardiac shunting:

$$ \mathrm{Cardiac}\ \mathrm{Output} = \frac{\mathrm{Oxygen}\\mathrm{consumption}}{\mathrm{arteriovenous}\ \mathrm{oxygen}\ \mathrm{difference}} $$.

or

$$ \mathrm{CO} = \frac{{\mathrm{VO}}_2}{\mathrm{Ca}-\mathrm{Cv}} $$.

PACs can directly obtain the pressure of the pulmonary artery in adults and children. This is often beneficial in patients with pulmonary hypertension though the risk in obtaining them especially in children is high (Carmosino et al. 2007). However, there currently are no other means to obtain accurate pressure measurements across the capillary bed, making placement a necessity. The PA catheter also has a balloon at the end and can be wedged in a peripheral pulmonary artery allowing for an indirect measurement of left atrial (LA) pressure. This can help decipher cardiac vs. noncardiac lung injury.

The placement of a PA catheter is generally safe but includes all the risk of IJV placement and additionally the increased risk of placing a large catheter from the right atrium across the tricuspid valve into the right ventricle and then into the pulmonary artery. Care should be taken not to cannulate or dilate the carotid artery as severe injury could occur due to the large sheath and catheter size. The placement of the catheter can cause conduction problems arrhythmias and injury to the valves and there are case reports of its knotting requiring surgical removal (Graybar et al. 1983; Perkin and Anas 2011). The most concerning complication is pulmonary artery hemorrhage that may occur when obtaining a wedge pressure. The hemorrhage is often difficult to stop and is a mortality risk (Hannan et al. 1984). A PA catheter may be placed directly by the surgeon in the operating room if that information is considered important for intra- and postoperative management. Depending upon the catheter type chosen it is possible to also make use of a continuous mixed venous oximetry catheter to be utilized to help guide postoperative inotropictransfusion and volume therapy or intermittent venous blood gases may be drawn to measure the mixed venous saturation.

PACs can give information that is difficult if not impossible to achieve through any other monitoring system. They are not without their risks, however, and these risks frequently outweigh any benefit in routine cardiac cases. There are certain patients and medical situations where a PAC is not only warranted but potentially required and great care should be used in its placement and interpretation

The PAC is floated right before bypass initiation with assistance by the surgeon guiding it manually to minimize the risk of arrhythmias during placement. The wedge pressure is 22 with PA pressures of 54/ 32 mean of 41 with a mean systemic pressure of 62. The wedge pressure is 8 with a mean PA pressure of 30 compared to the systolic mean of 58 after VAD initiation (*Fig. 2*)

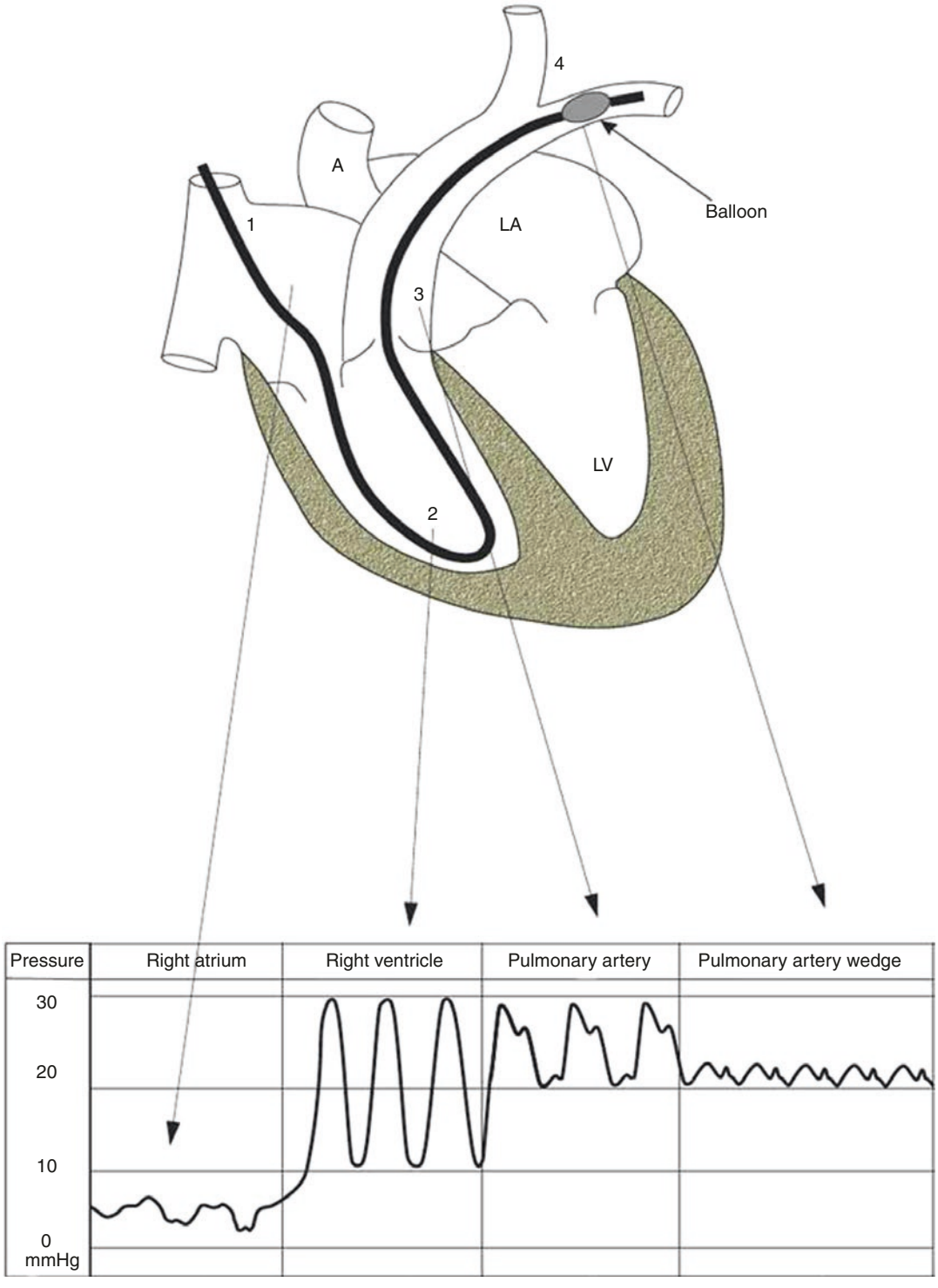


Fig. 2 A schematic presentation of the PAC course and its related pressure waveforms in cardiac chambers, pulmonary artery, and main left pulmonary artery (Modified from Dabbagh (2014). Published with kind permission of © Springer, 2014. All Rights Reserved)

Minimally Invasive Cardiac Output Monitors

Minimally invasive cardiac output monitors are defined as any device placed that can measure cardiac output without the placement of a PAC. The benefits of CO monitoring without the risks of PAC placement are very appealing. There are multiple devices that have been developed with a great deal of variability in their science and accuracy. Many of these devices require some invasive catheters including arterial, CVL, or both. We will discuss only a few on the many types of minimally invasive monitors in this chapter.

Pulse Contour Analysis

The most commonly used monitors evaluate pulse contour analysis and the systolic upstroke of an arterial line to obtain stroke volume. Pulse contour analysis monitors must be calibrated, and the two most common techniques use lithium or ice cold water to obtain a thermodilution baseline from CVL or peripheral IV[1] to arterial line. An algorithm is used, while the arterial waveform is continuously monitored, and the CO is displayed. These monitors are inaccurate when there is any dampening or resonance of the arterial signal and are also inaccurate with an aortic balloon pump, arrhythmias, or aortic insufficiency (Monnet et al. 2004; Hofer et al. 2007; Richard et al. 2011; Monnet and Teboul 2015). There is also a limited number of studies in the cardiac operating room, and only two studies involve pediatric cardiac patients (Mahajan et al. 2003; Sander et al. 2005, 2006; Fakler et al. 2007; Phan et al. 2011; Broch et al. 2015). The majority of these studies showed relative inaccuracies of the monitors compared to the gold standard methods (Fick or thermodilution). The risk factor of these catheters is minimal and is the same as the risk of the invasive lines needed for them.

[1]The LIDCO monitor uses lithium dilution and can be done via a peripheral line.

Ultrasound

The ultrasound technique of noninvasive cardiac monitoring is a by-product of the development of routine transesophageal echocardiography (TEE) used in cardiac and other major surgical cases. TEE is able to estimate CO by obtaining the instantaneous blood flow through a specific cross-sectional diameter of the descending aorta multiplied by the heart rate. The probes used in the minimally invasive technique are much smaller and portable compared to the TEE probes. Each has a different method in obtaining the flow and diameter, and general validation to the gold standard has been poor in most studies (Valtier et al. 1998; Chand et al. 2006; Chatti et al. 2009; Phan et al. 2011).

There is some benefit however in following trends despite the lack of absolute accuracy when compared to thermodilution. The major concerns are the toleration and difficulty with precise placement with the intraesophageal type. The extrathoracic version uses nomograms, which may further decrease accuracy. Both types use the assumption that blood flow is the same in the carotids and the descending aorta, which is not necessarily the case in sick patients (Marik 2013a). The studies in children are extremely poor with no studies including patients with shunts or significant congenital heart disease (Wongsirimetheekul et al. 2014; Beltramo et al. 2016). The risk factors for placement of these devices are minimal for the intraesophageal (similar to OG tube placement) and virtually nonexistent for the extrathoracic version.

Bioimpedance/Bioreactance

Bioimpedance cardiac monitors are the least invasive of the cardiac output devices discussed in this chapter. Electrodes are placed on a patient that both give and receive electrical signal. The primary component of variable impedance (what is altering the signal) is blood flow in the aorta. An algorithm is used to compute the cardiac output from this change in impedance. These monitoring devices would seem to have the poorest

correlation with the gold standard of thermodilution (Marik et al. 1997; Critchley et al. 2000; Spiess et al. 2001; Sageman et al. 2002; Gujjar et al. 2008). Pediatric studies have used these devices clinically, showing CO changes with interventions and correlation with TEE, but there was a poor correlation with thermodilution (Schubert et al. 2008; Cote et al. 2015). The placement of these devices involves simple electrodes and is without any significant risk.

Minimally invasive cardiac output monitors are being used in many patients with variable diseases and ages. Their accuracy and validity are questioned when compared to the gold standard, but new algorithms have improved some of these concerns. They have yet to be considered part of the routine management for pediatric or adult cardiac patients.

At this time, a monitor that is without flaws and that will diagnose the hemodynamic variable that it is monitoring has not been developed. The practitioner must understand how a specific monitor works and its limitations and the risks with its placement before deciding on its use. The interpretation of the monitor and the practitioners' response will always be the most important component in patient management (Tables 3 and 4).

Table 3 Normal range of blood pressure in *BOYS* with special focus on " *The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents*" of the " *National High Blood Pressure Education Program Working Group on High Blood* Pressure in Children and Adolescents" (McLain 1976; Blumenthal et al. 1977; Horan and Sinaiko 1987; Feld and Springate 1988; Brzezinski 1990; Zubrow et al. 1995; Bartosh and Aronson 1999; 2004; Dionne et al. 2012; Bonafide et al. 2013; Heys et al. 2013; Shieh et al. 2013; Bassareo and Mercuro 2014; Ingelfinger 2014; Shah et al. 2015)

	DBP mm Hg		SBP mm Hg		MAP mm Hg	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	34–39	54–58	80–89	98–106	49–55	69–75
2	39–44	59–63	84–92	101–110	54–60	73–79
3	44–48	63–67	86–95	104–112	58–64	77–82
4	47–52	66–71	88–97	106–115	61–67	79–86
5	50–55	69–74	90–98	108–116	63–69	82–88
6	53–57	72–76	91–100	109–117	66–71	84–90
7	55–59	74–78	92–101	110–119	67–73	86–92
8	56–61	75–80	94–102	111–120	69–75	87–93
9	57–62	76–81	95–104	113–121	70–76	88–94
10	58–63	77–82	97–106	115–123	71–77	90–96
11	59–63	78–82	99–107	117–125	72–78	91–97
12	59–64	78–83	101–110	119–127	73–79	92–98
13	60–64	79–83	104–112	121–130	75–80	93–99
14	60–65	80–84	106–115	124–132	76–82	95–100
15	61–66	81–85	109–117	126–135	77–83	96–102
16	63–67	82–87	111–120	129–137	79–85	98–104
17	65–70	84–89	114–122	131–140	81–87	100–106

Table 4 Normal range of blood pressure in *GIRLS* with special focus on " *The fourth report on the diagnosis, evaluation, and treatment of high blood pressure in children and adolescents*" of the " *National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents*" (McLain 1976; Blumenthal et al. 1977; Horan and Sinaiko 1987; Feld and Springate 1988; Brzezinski 1990; Zubrow et al. 1995; Bartosh and Aronson 1999; National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents 2004; Dionne et al. 2012; Heys et al. 2013; Bassareo and Mercuro 2014; Ingelfinger 2014; Shah et al. 2015)

	DBP mm Hg		SBP mm Hg		MAP mm Hg	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	38–42	56–60	83–90	100–107	53–58	71–76
2	43–47	61–65	85–91	102–109	57–62	75–80
3	47–51	65–69	86–93	104–110	60–66	78–83
4	50–54	68–72	88–94	105–112	63–67	80–85
5	52–56	70–74	89–96	106–114	64–69	82–87
6	54–58	72–76	91–98	108–115	66–71	84–89
7	55–59	73–77	92–101	110–119	67–73	85–91
8	57–60	75–78	94–102	111–120	69–74	87–92
9	58–61	76–79	95–104	113–121	70–75	88–93
10	59–62	77–80	97–106	115–123	72–77	90–94
11	60–63	78–81	99–107	117–125	73–78	91–96
12	61–64	79–82	102–109	119–126	75–79	92–97
13	62–65	80–83	104–110	121–128	76–80	94–98
14	63–66	81–84	106–112	123–129	77–81	95–99
15	64–67	82–85	107–113	124–131	78–82	96–100
16	64–68	82–86	108–114	125–132	79–83	96–101
17	64–68	82–86	108–115	125–132	81–84	96–101

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Electrocardiography: Basic Knowledge with Focus on Fetal and Pediatric ECG

Majid Haghjoo and Mohammadrafie Khorgami

Abstract

Although the basic principles of electrocardiogram (ECG) interpretation in children are identical to those in adults, pediatric ECGs are more challenging to read as compared to adult ECGs. These difficulties are mainly related to progressive changes in normal cardiac anatomy and physiology between birth and adolescence. Furthermore, structural and hemodynamic changes in congenital heart disease may affect nearly all aspects of the surface ECG. Therefore, the ability to clearly distinguish an abnormal ECG pattern from a normal variant is an essential skill for pediatric practitioners. The purpose of this chapter is to provide a systematic approach to ECG interpretation in pediatric patients. We also discussed all important ECG abnormalities such as chamber hypertrophy, conduction abnormalities, and common cardiac arrhythmias. In addition, we presented typical ECG features of common congenital heart diseases, cardiomyopathies, cardiac inflammatory conditions, and cardiac tumors in children. We hope that the readers will find this chapter a helpful synopsis and an enjoyable experience.

Keywords

Electrocardiography · Pediatric · Fetal · Congenital · Rhythm · Tachyarrhythmia · Dystrophy · Tumor · Cardiomyopathy

Although the basic principles of electrocardiogram (ECG) interpretation in children are identical to those in adults, pediatric ECGs are more challenging to read as compared to adult ECGs. These difficulties are mainly related to progressive changes in normal cardiac anatomy and physiology between birth and adolescence. Furthermore, structural and hemodynamic changes in congenital heart disease (CHD) may affect nearly all aspects of the surface ECG.

There are many reasons for ECG recording in children, including chest pain, syncope, and suspected arrhythmia. Recording an artifact-free ECG is the first step in the correct interpretation of the pediatric ECGs. This may be a real challenge in agitated infants or active children. To obtain an artifact-free ECG recording, distractors such as cartoons, movies, and stickers would be highly helpful. Some children in the outpatient setting have sinus tachycardia due to anxiety that should be taken into consideration. Because of right ventricular (RV) dominance in infancy, some pediatric cardiologists prefer to obtain 15-lead ECG, including leads V3R, V4R, and V7. The normal neonatal ECG has more high-

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frequency details because of higher voltage and shorter QRS duration; therefore, American Heart Association recommended 150 Hz for minimum bandwidth cutoff and 500 Hz for minimum sampling rate (Bailey et al. 1990).

The second step in correct pediatric ECG interpretation is to consider the clinical condition at the time of recording. Many of the noncardiac diseases in children may have important effects on the normal ECG; therefore, abnormal ECGs do not always equal heart disease.

The normal ECG values in pediatric are age- and heart rate-dependent. The most changes occur in the first year of life. In fetal life, the circulatory system is primarily dependent on the RV. As a result, at birth, the RV is larger and thicker than the left ventricle (LV). This produces an ECG pattern reminiscent of RV hypertrophy (RVH) in adults. During infancy, a progressive decrease in pulmonary vascular resistance and closure of PDA shifts physiological stress to the left side, and the LV force become predominant by 6 months (O'Connor et al. 2008).

The systematic approach for pediatric ECG interpretation includes evaluation for heart rate, rhythm, QRS axis, conduction intervals, chamber hypertrophy, and enlargement.

Heart Rate

The heart rate variation during childhood is significant. The age, body mass index, metabolic states, and other variables influence the heart rate. The standard ECG is usually recorded at a paper speed of 25 mm/s, therefore, a small box equals 0.04 s (40 ms) and a large box equals 0.2 s (200 ms). Atrial and ventricular rates should be calculated separately if they are different. There are several methods for calculating heart rate (Fig. 1):

1. Dividing the number of large boxes between two consecutive R waves by 300.
2. Dividing the number of small boxes between two consecutive R waves by 1500.
3. Dividing R-R interval (in ms) by 60,000.
4. For irregular rhythms: multiplying the number of QRS complexes recorded during the 10-s rhythm strip by 6.

Neonatal heart rate varies between 150 and 230 beats/min, especially during crying. The heart rate reaches a peak between one and two months of life and then decreases gradually until six months. Between six months and the first year

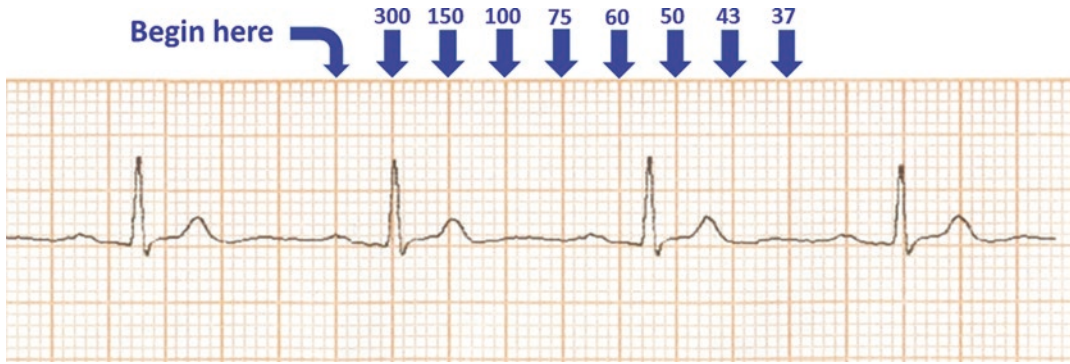

Fig. 1 Rapid heart rate calculation by dividing the number of large boxes between two consecutive R waves by 300

of life, it tends to reach a plateau and after that, it decreases gradually to reach the adult heart rate (Schwartz et al. 2002).

Rhythm

For the determination of heart rhythm, it is important to determine the exact origin of cardiac impulses. During normal sinus rhythm (NSR), the sinus node is responsible for electrical impulse generation. This impulse depolarized atrial myocytes from the superior-right to the inferior-left direction. Consequently, the P-wave axis would be between zero and + 90 degrees and the P-wave morphology would be positive in leads I, II, and aVF and biphasic in lead V1. If the P-wave origin is from other atrial locations, the P-wave morphology would be different; for example, left atrial rhythm shows a negative P-wave in leads I and aVL and low RA rhythm exhibits a negative P-wave in leads II, III, and aVF. Therefore, NSR is characterized by a normal P-wave (positive I, II, and aVF) before each QRS complex with a constant PR interval, and a heart rate within the normal range for age.

QRS Axis

The frontal QRS axis vector is the means of the direction of the ventricular wavefronts in the frontal plane. There are several methods to estimate the QRS axis:

1. *Quadrant method*: polarity of QRS complexes in leads I and aVF is determined. Based on the polarity of these two leads, four quadrants and the corresponding QRS axis are defined. If the leads I and aVF are both positive, the axis is normal. Otherwise, there is some kind of axis deviation. Negative QRS in both leads indicates an "extreme axis deviation." Positive QRS in lead I and negative in lead aVF points to a possible left axis deviation (LAD) and reverse configuration shows right axis deviation (RAD) (Fig. 2).
2. *Isoelectric lead*: Isoelectric lead is characterized by either a biphasic QRS with equal R- and S-wave amplitude or a flat-line QRS. If the QRS is isoelectric in any given lead, the axis is perpendicular to this lead.
3. *Positive lead*: Another method is to find the lead with the tallest R-wave. The axis is roughly in the same direction as this lead.

The normal neonatal QRS axis is between +55 and +200 because of RV dominancy and decreases to +160 by one month. However, in the preterm infant, the normal frontal axis is between +65 and +174 (Schwartz et al. 2002). Parallel to cardiac changes during the first 1–3 years of life, the ECG pattern changes from RV dominance to LV dominance. As a result, the QRS axis will shift from the right to the more leftward axis (−30 to +100) (O'Connor et al. 2008).

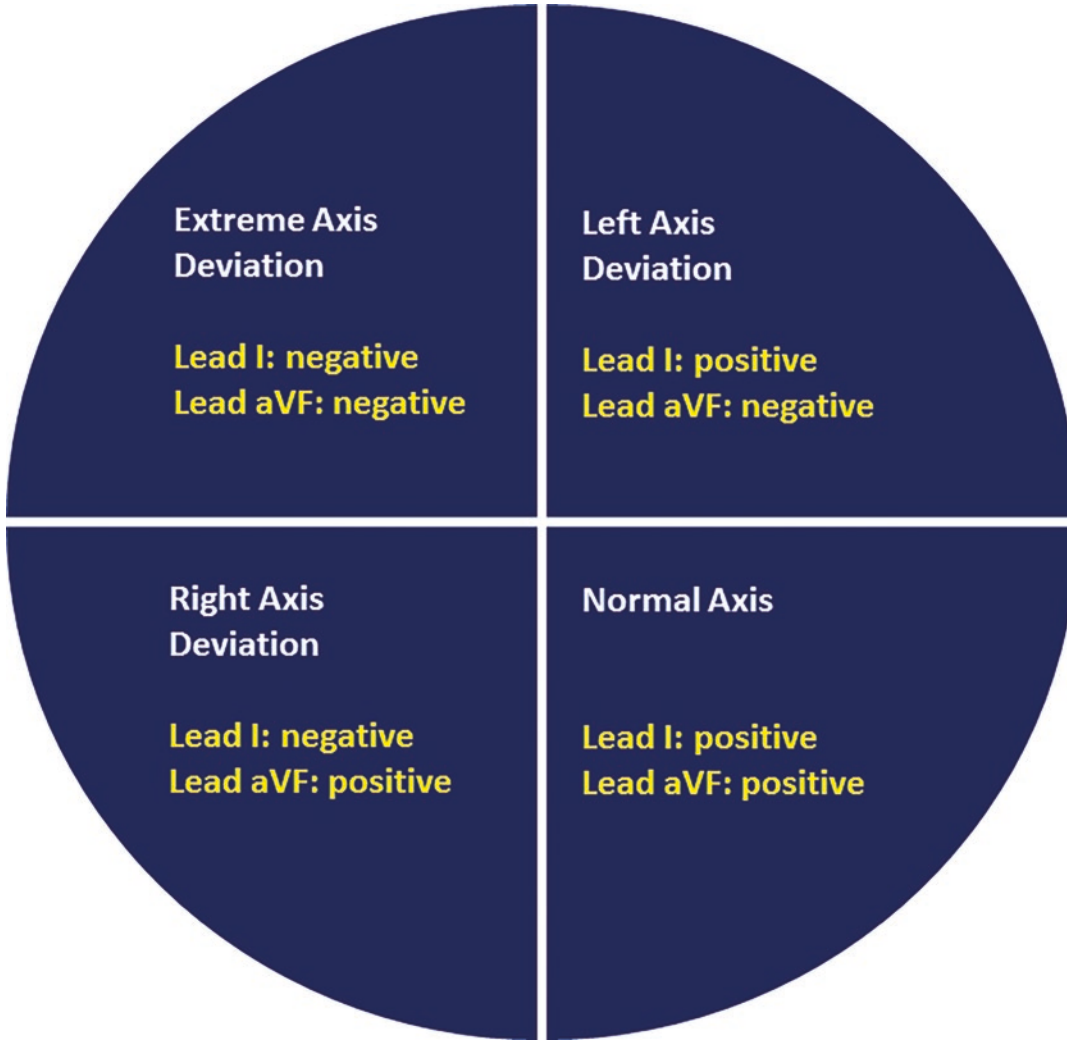

Fig. 2 QRS axis determination by quadrant method

Conduction Intervals

PR Interval

The PR interval represents electrical impulse conduction from the sinus node through the atria, atrioventricular (AV) node, His bundle, bundle branches, and Purkinje system to ventricular myocyte (Fig. 3). PR interval is measured from the onset of P-wave to the onset of QRS complex, usually in lead II. Normal AV conduction is defined as normal PR interval and normal association of each P-wave to the following QRS complex.

Normal PR interval duration is shorter in children and changes with age and heart rate. This finding may be due to the smaller cardiac mass in children. The neonatal PR interval may vary between 70 ms and 140 ms with a mean of 100 ms (Schwartz et al. 2002). Therefore, AV conduction abnormality in young children may present with normal-appearing PR interval.

Short PR interval indicates that impulse generates from locations other than normal pace-

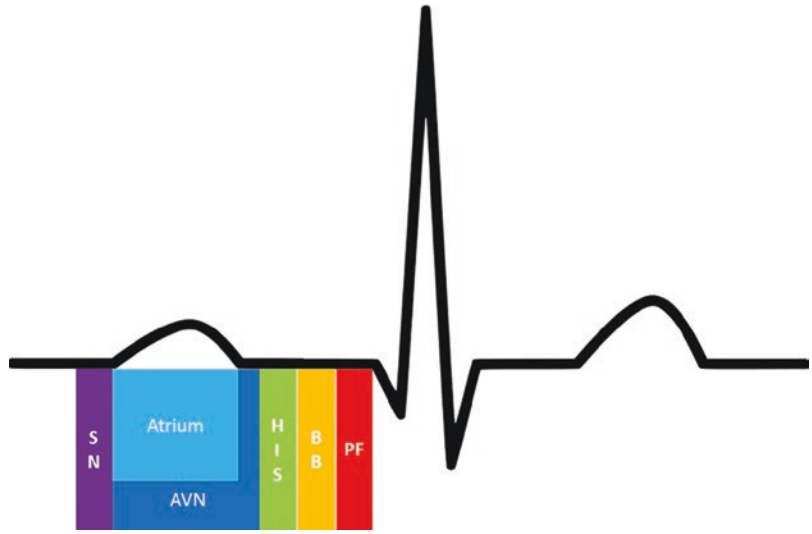

Fig. 3 PR interval components

maker (sinus node), presence of accessory AV connections, or facilitated AV node conduction. PR prolongation represents impaired AV conduction. Injury to normal conduction pathway in the atrium, AV node, His bundle, and bundle branches could increase PR duration.

For PR analysis, the association of each QRS to the previous P-wave is necessary. P-QRS evaluation in consecutive beats could help us to detect dissociation of the P-wave and QRS complex in disorders such as junctional rhythm and AV blocks.

QT Interval

QT interval reflects both ventricular depolarization and repolarization. It is measured from the onset of the Q-wave to the end of the T-wave usually in leads II, V5, or V6 (Schwartz et al. 2002). QT is age and heart rate-dependent. The increase in heart rate results in a shorter QT interval. In the cases where T- and U-waves overlap and discrimination of two waves is difficult or P wave superimposes on T-wave (usually in the infant with higher heart rate), a line is drawn from the peak of the T-wave tangential to its downslope until it intersects the isoelectric line and this point is considered as the end of T-wave (Fig. 4).

For the elimination of RR interval variation on QT interval, QT should be corrected (QTc). Bazett's formula is a practical method for QTc calculation: QTc = QT interval (ms)/$\sqrt{}$R–R interval (sec) (Bazett 1920). For patients with intraventricular conduction delays (paced rhythms or bundle branch block), a modified QTc was calculated using the formula: modified QTc = (QT-(QRS-120))/$\sqrt{}$RR (Patel et al. 2015).

Multiple studies were done to the determinate cutoff point for QT prolongation. In the first few days of the neonatal period, the upper limit (2 standard deviations above the mean or 97.5 percentile) for QTc is 440 ms. After this period, there is an increase in QT interval duration; In the first six-month of life, the QTc interval can be as long as 490 ms, however, after 6 months the cutoff point for normal QTc is 440 ms (O'Connor et al. 2008). Anyway, if the QTc is greater than 50% consecutive R-R interval, it is considered abnormal.

The QT interval calculation is important because the presence of long QT predisposes the patients into malignant arrhythmia, i.e., torsades de points. The QT prolongation may have congenital and acquired types (Fig. 5). Before evaluation for congenital disorders acquired causes such as drugs and electrolyte abnormalities should be ruled out.

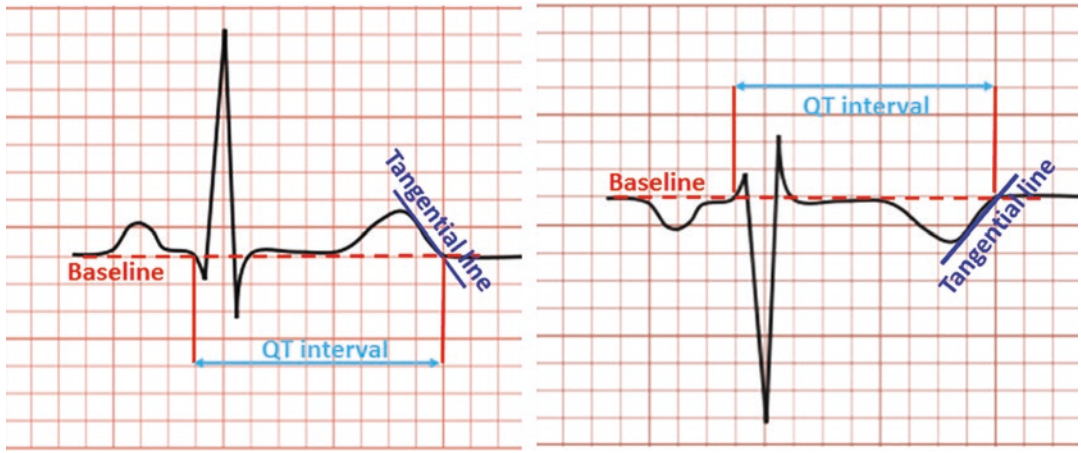

Fig. 4 QT measurement using the tangential method. In this method, the end of the T wave is determined by the intersection of a tangent line extrapolated from the T wave at the point of maximum downslope to the isoelectric baseline

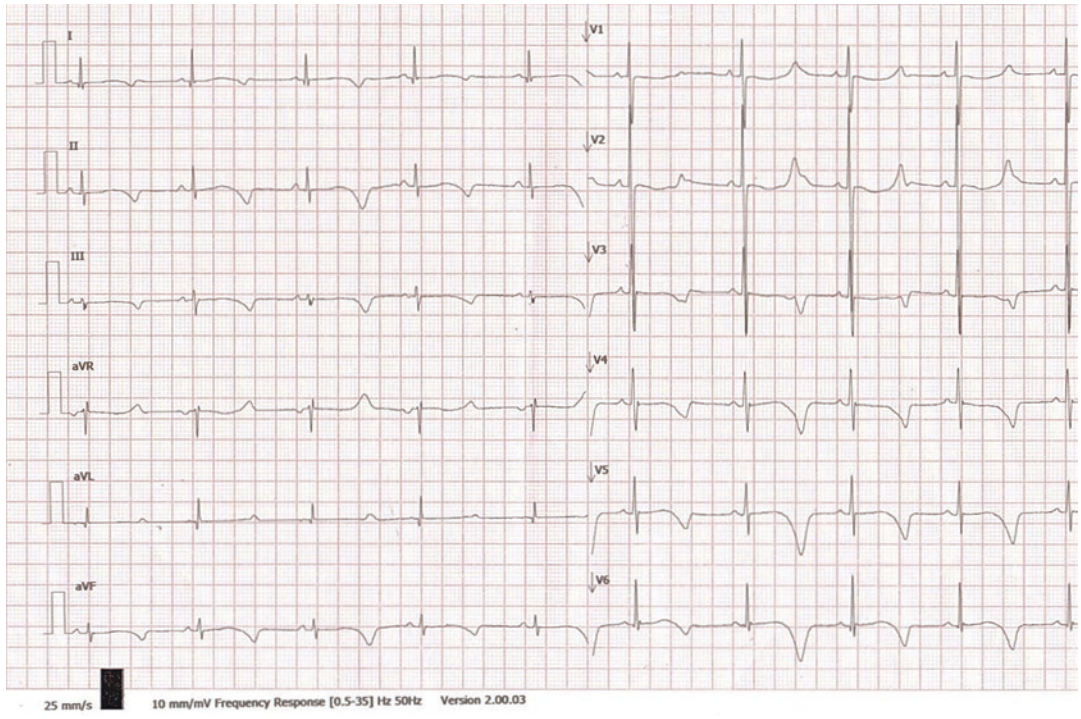

Fig. 5 Congenital long QT syndrome. Extreme QT prolongation (QTc = 600 ms) with macroscopic T-wave alternans (more prominent in precordial leads)

Morphology

P-Wave

The P-wave displays atrial depolarization. The first 0.04–0.06 s of the P-wave is related to RA depolarization and the remainder is related to the LA. RA enlargement is defined as a tall and peaked P-wave in lead II. In infants and children, the P-wave amplitude greater than 2.5–3.0 mV is considered abnormal. LA enlargement is characterized by a broad (≥ 0.12 s) and notched P-wave in lead II or wide (>0.04 s) and deep (>0.1 mV) terminal component (negative phase) in lead V1. In biatrial enlargement, both criteria for atrial enlargement are present.

QRS Complex

Measurement of R-wave amplitude and QRS duration especially in precordial leads reflect ventricular depolarization status. Because of lower ventricular mass, the QRS duration is usually shorter in children than in adults: under 4 years of age, it is less than 0.09 s, less than 0.10 s up to 16 years of age, and less than 0.11 s by late adolescence (Deal et al. 2004).

Thin chest and proximity of heart to ribs in neonate cause tall R- or S- wave in precordial leads in comparison to limb leads. Low QRS voltage may indicate myocarditis, pericardial effusion, and hypothyroidism.

Fetal circulation is mainly dependent on RV function, therefore, in the neonatal period, RV muscle mass increased in comparison to LV. This change on surface ECG reflects as high amplitude R-wave in the right precordial lead with R/S > 1 and a deep S-wave in left precordial leads with R/S < 1. Gradually after 1 month, the RV loses its dominancy and the LV is the dominant ventricle by the end of the first year of life. As a result, the R-wave amplitude will decrease in right precordial leads and increase in left precordial leads with advancing age (S wave changes are reversed). Therefore, age-related R- and S-wave amplitude changes in precordial leads should be considered while assessing the ECG for ventricular hypertrophy.

T-Wave

The T-wave morphology and axis are changing during childhood. T-wave represents ventricular repolarization. As opposed to ventricular depolarization, repolarization begins from the epicardium to the endocardium (QRS-T axis concordance). More than 90 degrees difference between two axes may indicate myocardial injury. The T-wave amplitude value may vary from 0.5 mV in limb leads up to 10 mV in precordial leads (Coviello Shank 2016).

In the first week of life, T-wave is upright in leads V1 and V3R. Then, it becomes inverted until 8 years and even maybe continued to adolescence. In the first 3–5 years of life, 50% of children have inverted T-wave in lead V2 but this value decreases to 5–10% in 8–12 years (Dickinson 2005). Persistent positive T-wave after the first week may represent RVH. T-wave is usually positive in left precordial leads in childhood except for the first few days of life that T-wave may be flat or inverted. Although ST-T segment changes are nonspecific evaluation for diseases such as myocarditis, cardiomyopathy, pericarditis, and electrolyte disorders should be done.

In children especially during tachycardia, P-wave may be superimposed on T-wave. A comparison of serial T-wave morphology in the long strip of the ECG may be helpful. Notched T-wave in leads V2 and V3 can be a normal variant in children. It may be misdiagnosed with 2:1 atrioventricular block but with careful examination, this pattern is not observed in other leads. Hyperkalemia causes tall and peaked T wave (tented T-wave) in surface ECG.

ST Segment

It measured from the end of the QRS complex to the onset of the T-wave. J-point is the beginning of the ST segment. It represents the termination of depolarization with the onset of ventricular repolarization. It is elevated when it is at least 1 mm above the isoelectric line and depressed when it is 0.5 mm below the isoelectric line (Deal et al. 2004). ST-segment elevation as J-point elevation is very common in adolescents. It is related to early depolarization and may be considered in the differential diagnosis of other diseases especially pericarditis. In early repolarization, ST segment returns to the baseline with exercise. Early repolarization is usually better observed in mid-precordial leads. Special forms of early repolarization may be a risk factor for sudden death. ST-segment elevation in children is usually related to pericarditis, however, less common causes such as myocardial ischemia should be considered.

Chamber Hypertrophy

Right Ventricular Hypertrophy

RVH in children mostly results from congenital heart diseases with pressure- and volume-overload mechanisms. Other causes include cardiomyopathy, hereditary myocardial disease, pulmonary vascular disease, and respiratory disease.

The ECG criteria for RVH (Table 1) include R wave >98th percentile in V1, S wave >98th percentile in V6, R/S ratio >98th percentile in V1, RAD according to age, upright T-wave in V1 between the first week and 8 years, specific morphologies of QRS (R, QR, RsR) in right precordial leads, neonatal R-wave progression in precordial leads in older children (Fig. 6) (Davignon et al. 1979). As a criterion for RVH, RAD should be considered with other criteria. In combination with right atrial enlargement and deep S-wave in V6, Cor pulmonale should be suspected.

Diagnosis of RVH in the neonate may be difficult but signs of RVH include: QR complex in V1, upright T-wave in V1 after the first week of life, increased R-wave amplitude in V1, and decreased S-wave amplitude in V6.

Left Ventricular Hypertrophy

Left ventricular hypertrophy (LVH) interpretation at surface ECG is based on voltage and repolarization criteria. ECG criteria of the LVH (Table 2) include R-wave >98th percentile in V6,

Table 1 Right ventricular hypertrophy voltage criteria

R wave >98th percentile in lead V1
S wave >98th percentile in lead V6
R/S ratio >98th percentile in lead V1
Right axis deviation (>98th percentile of QRS in the frontal plane)
Upright T wave in V1 (1 week old to 8 years old)
qR pattern in V1
RSR' pattern in lead V1, where R′ > 15 mm (<1 year old) or R′ > 10 mm (>1 year old)
Neonatal R-wave progression in precordial leads in older children

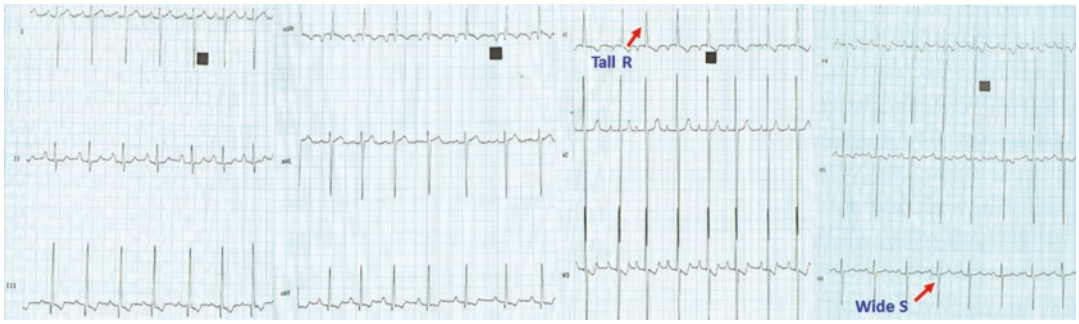

Fig. 6 Right ventricular hypertrophy. Typical ECG features are tall R wave in V1, deep S wave in V6, and right axis deviation

Table 2 Left ventricular hypertrophy voltage criteria.

R-wave >98th percentile in lead V6
S-wave >98th percentile in lead V1
R/S ratio >98th percentile in lead V6
Q-wave >98th percentile in lead V6 or lead III
Inverted T-wave in left precordial leads
Increased T-QRS angle (>100 degrees)
Increased inferior forces
Decreased RV dominancy (neonate)
Normal adult ECG pattern (neonate)

S-wave >98th percentile in V1, R/S ratio >98th percentile in V6, Q-wave >98th percentile in V6 or lead III, inverted T-wave in left precordial leads, increased T-QRS angle (>100 degrees), and increased inferior forces (low specificity) (Fig. 7).

In normal conditions, T-wave and QRS complex axes have similar directions, but two axes would shift to opposite directions in LVH. It is

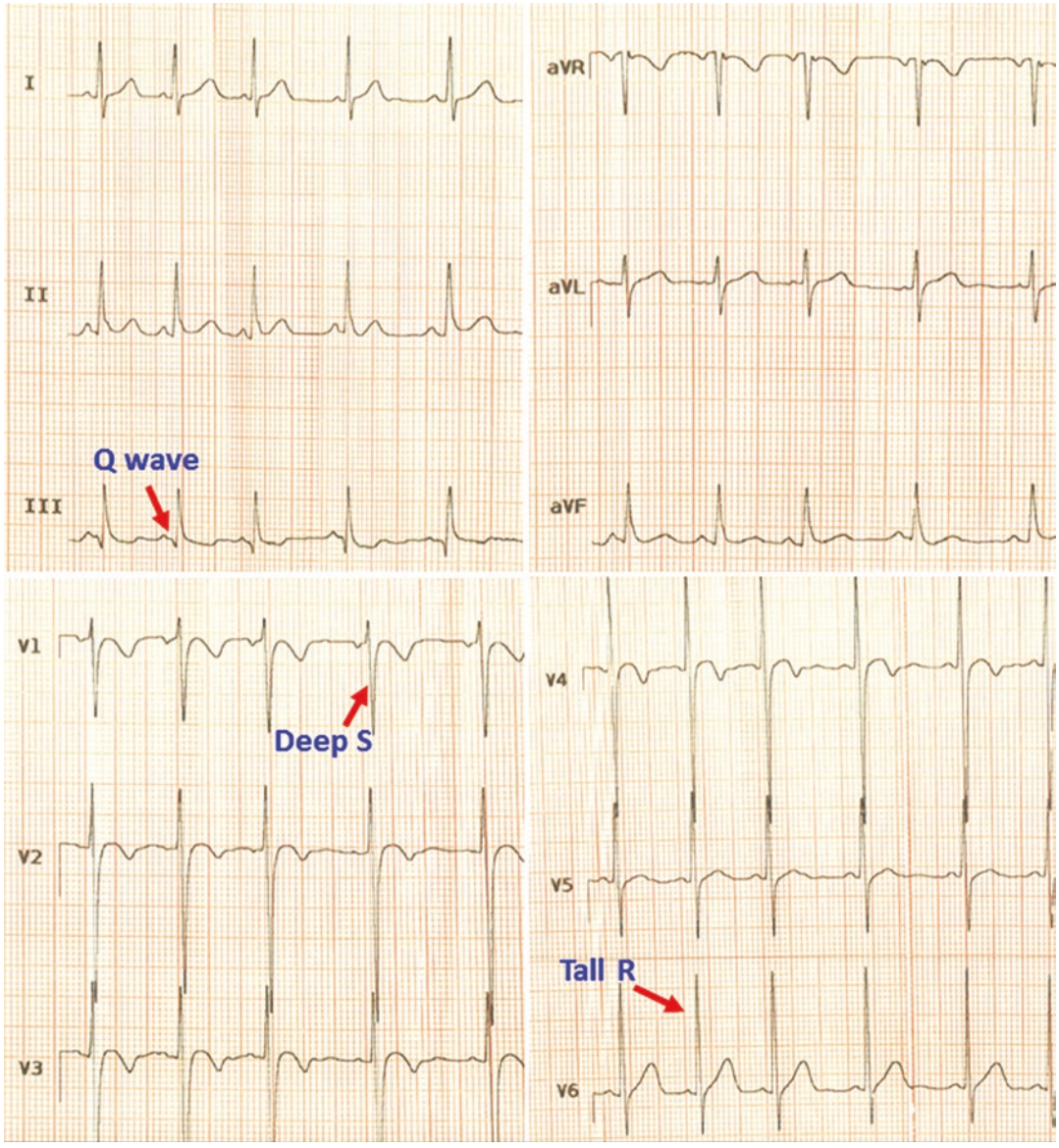

Fig. 7 left ventricular hypertrophy. Typical ECG features consist of tall R wave in V6, deep S wave in V1, Q wave in lead III, and increased inferior forces

Table 3 Biventricular hypertrophy voltage criteria.

Increased R-wave and S-wave voltages in lead V1 and lead V6
High amplitude R- and S-wave in mid-precordial leads
Combination of R- and S-wave amplitudes in leads V3 or V4 > 60 mm

important to note that LAD in children is not a criterion for LVH. Although ST-segment and T-wave changes are nonspecific markers for the myocardial disease but should be considered as the signs of LVH after excluding ischemic and myocardial diseases.

In neonates, the decreased RV dominancy may be the only sign of LVH, therefore, a normal adult ECG pattern in the neonate is indicative of the LVH. Of course in the preterm infant, the LV force is more prominent.

Biventricular Hypertrophy

Biventricular hypertrophy (BiVH) should be considered when criteria for both RVH and LVH are present (Table 3). In BiVH, increased R-wave and S-wave voltages are observed leads V1 and V6. High amplitude R- and S-wave in mid-precordial leads may be seen in children with a thin chest wall. If the combination of R- and S-wave amplitudes in leads V3 or V4 is more than 60 mm, BiVH should be considered (Katz and Wachtel 1937).

Conduction Abnormalities

Atrioventricular Block

AV block can occur in children as well as in adult. Underlying causes may be congenital or acquired. The acquired causes include surgical repair of congenital heart disease, cardiac catheterization, and infectious and inflammatory cardiac disease. Based on the severity of conduction system disease, AV block is divided into first, second, and third degree.

First-degree AV block, defined as PR interval prolongation, is a benign condition in children. As it was mentioned before, the PR interval is shorter in children than in adults, therefore, a normal-appearing PR interval may be indicative of conduction system disease. This form of AV block is usually asymptomatic and no treatment is necessary (Fig. 8).

Second-degree AV block is characterized by an intermittent failure of atrial impulse conduction to the ventricles (Fig. 9). There are two types of second-degree AV block: Mobitz type I (Wenckebach) and Mobitz type II. Mobitz type I AV block is defined as progressive prolongation of AV conduction leading up to a non-conducted P-wave. This kind of AV block is usually located in the AV node and needs no treatment. Mobitz type II AV block is present when there is a sudden loss of AV conduction without prior PR elongation. This type of AV block is usually located more distally in the His bundle, bundle branches, and Purkinje system. The treatment is pacemaker implantation.

Third-degree or complete AV block is presented by a lack of association between atrial and ventricular depolarization (Fig. 10). In this situation, atrial activity will be faster than ventricular response with no clear association. The treatment is pacemaker implantation.

Intraventricular Conduction Defect

His bundle is divided into left and right bundle branches. The left bundle is a sheet-like structure that is divided into the left anterior fascicle and the left posterior fascicle. The right bundle branch is a cord-like structure that runs along with the moderator band to the anterior portion of RV. Impulse conduction in the left bundle and its branches is faster compared with the right-sided counterpart. Consequently, depolarization of both ventricles is nearly simultaneous and the QRS complex is narrow. Injury to bundle branches may cause ventricular conduction delay and wide QRS.

Right Bundle Branch Block

In the right bundle branch block (RBBB), RV depolarizes through the myocardium, therefore, ventricle depolarization is sequential from LV to RV through the interventricular septum. Normal LV conduction gives rise to the normal initial

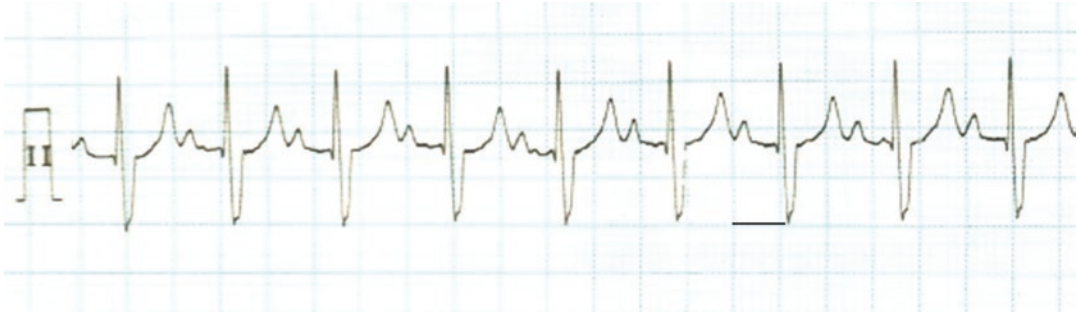

Fig. 8 First-degree atrioventricular block is characterized by PR interval prolongation (more than 200 ms)

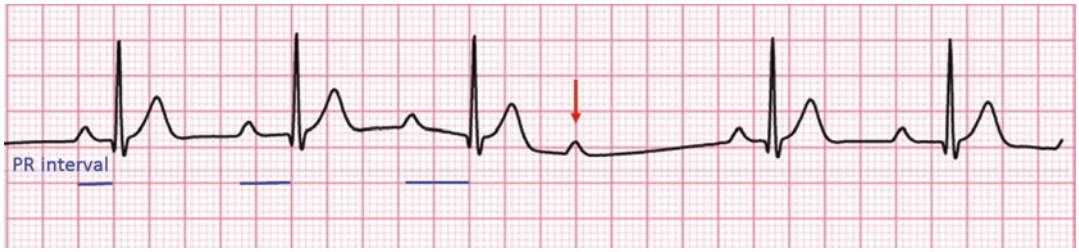

Fig. 9 Mobitz type I AV block is characterized by progressive prolongation of atrioventricular conduction leading up to a nonconducted P-wave (red arrow)

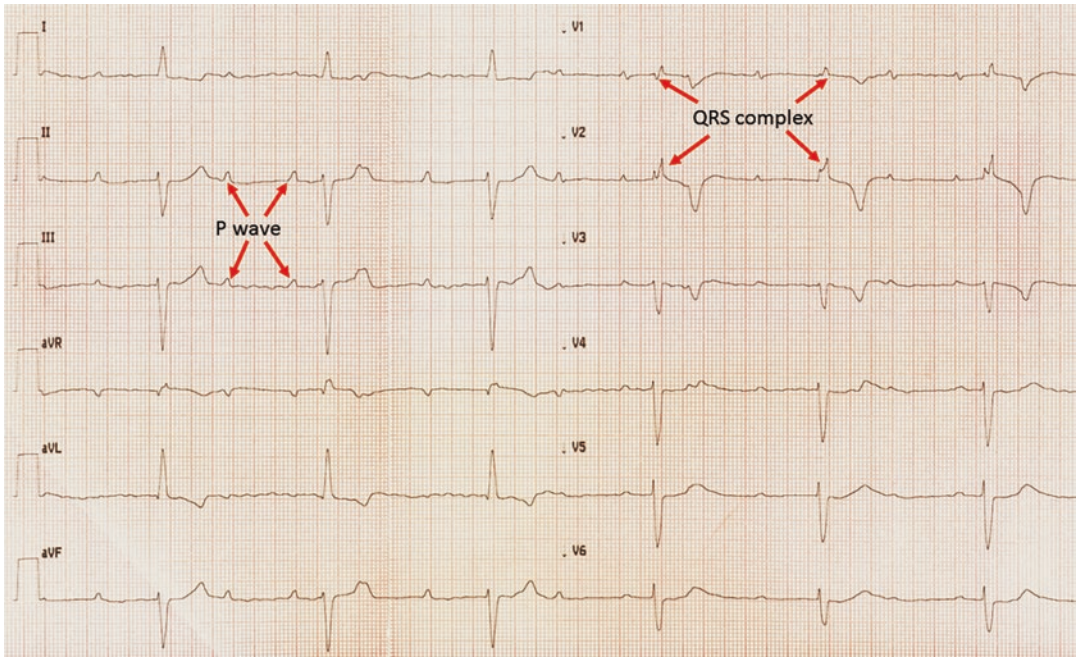

Fig. 10 Complete atrioventricular block presented by lack of association between atrial (P waves) and ventricular depolarization (QRS complexes)

component of QRS but the second component is slurred and wide due to delayed RV activation.

ECG characteristics of RBBB include: wide QRS according to age, rsR' in V1, wide S-wave in lead I, inferior leads, and left precordial leads (Table 4).

Table 4 Right bundle branch block criteria.

Wide QRS according to age
rsR′ in V1
Wide S-wave in lead I, inferior leads, and left precordial leads

Surgical closure of congenital heart disease especially VSD closure in tetralogy of Fallot is the most common cause of RBBB (Fig. 11). Compared with RBBB in the adult population, usually, there is no inverted T-wave and ST-segment depression. Isolated rsR' pattern with normal QRS complex duration in right precordial leads termed incomplete RBBB. This pattern doesn't necessarily implicate disease and may be seen in normal children but evaluation for atrial septal defect (ASD) should be considered.

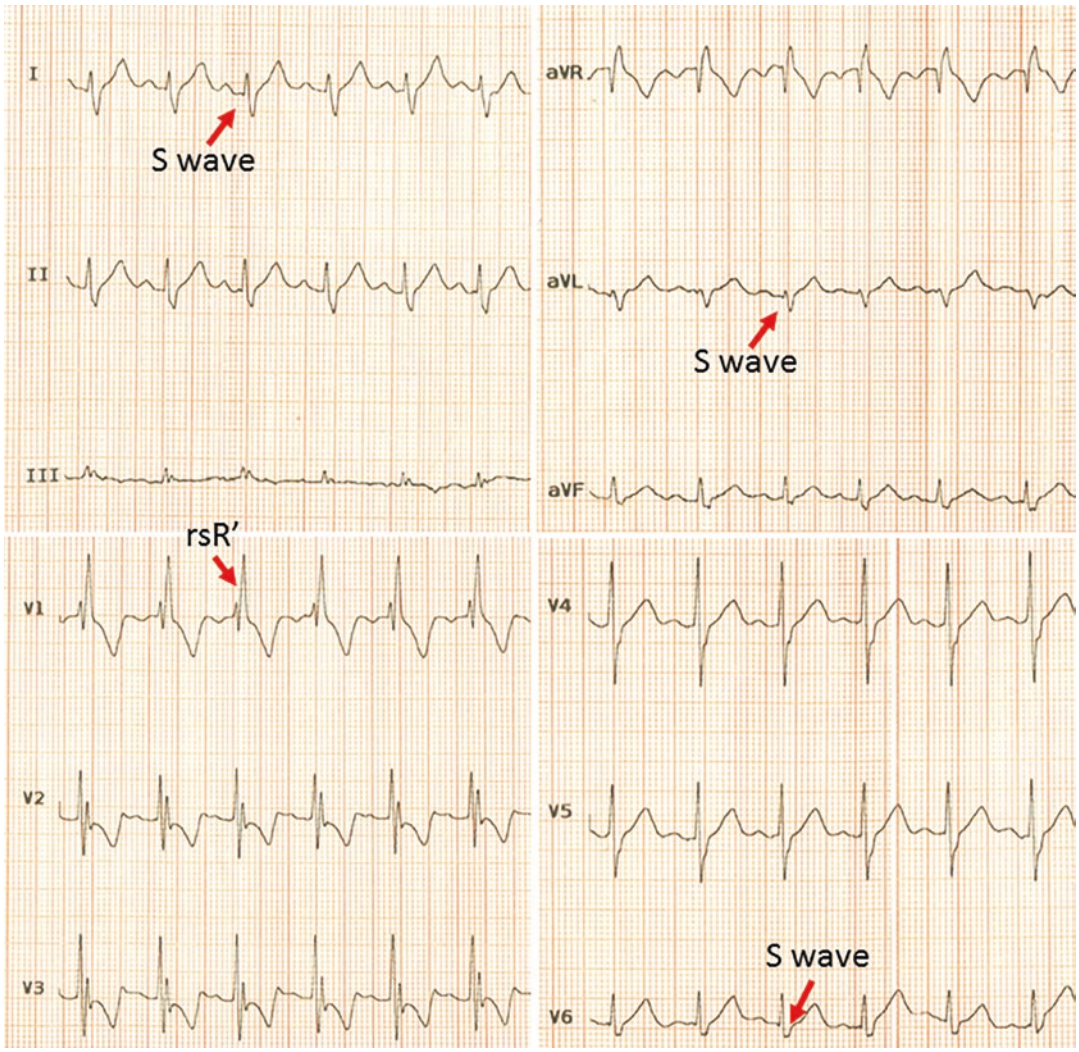

Fig. 11 Right bundle branch block. Note that there is rsR' in lead V1 and deep S waves in leads I, aVL, and V6

Left Bundle Branch Block

In the left bundle branch block (LBBB), interventricular depolarization is from right to left in a reverse manner and initial force (q wave) in left precordial leads is not observed. Because of LV anatomical position, slow conduction direction is left and posteroinferior.

ECG characteristics of LBBB (Table 5) include: wide QRS according to age, absent q-wave in leads V5 and V6, notched slurred R in leads I, aVL, V5, and V6, broad S-wave in leads V1 and V2, ST depression with inverted T-wave in left precordial leads (Fig. 12). LBBB is less common than RBBB. The most common cause is the aortic valve and left ventricular outflow tract (LVOT) surgical repair. Other causes include hypertrophic cardiomyopathy, dilated cardiomyopathy, and myocarditis.

Table 5 Left bundle branch criteria.

Wide QRS according to age
Absent q-wave in leads V5 and V6
Notched slurred R in leads I, aVL, V5, and V6
Broad S-wave in leads V1 and V2
ST depression with inverted T-wave in left precordial leads

Left Fascicular Block

Left anterior hemiblock (LAHB) is rare in children. In this type of block, QRS is normal. The last portion of LV depolarization is directed toward the anterosuperior region and, therefore, causes LAD and rS patterns in inferior leads. Some causes of LAHB include ventricular septal defect (VSD) closure, LVOT surgical repair, tricuspid atresia, endocardial cushion defects, and cardiomyopathy. LAHB diagnosis in infants needs serial ECG evaluation.

In the left posterior hemiblock (LPHB), LV depolarizes from an anterosuperior to posteroinferior direction. The ECG characteristics of LPHB include normal QRS duration, RAD (RVH should be ruled out), and QS pattern in inferior leads.

Multifascicular Block

The bifascicular block refers to the presence of conduction abnormality in two of the three main

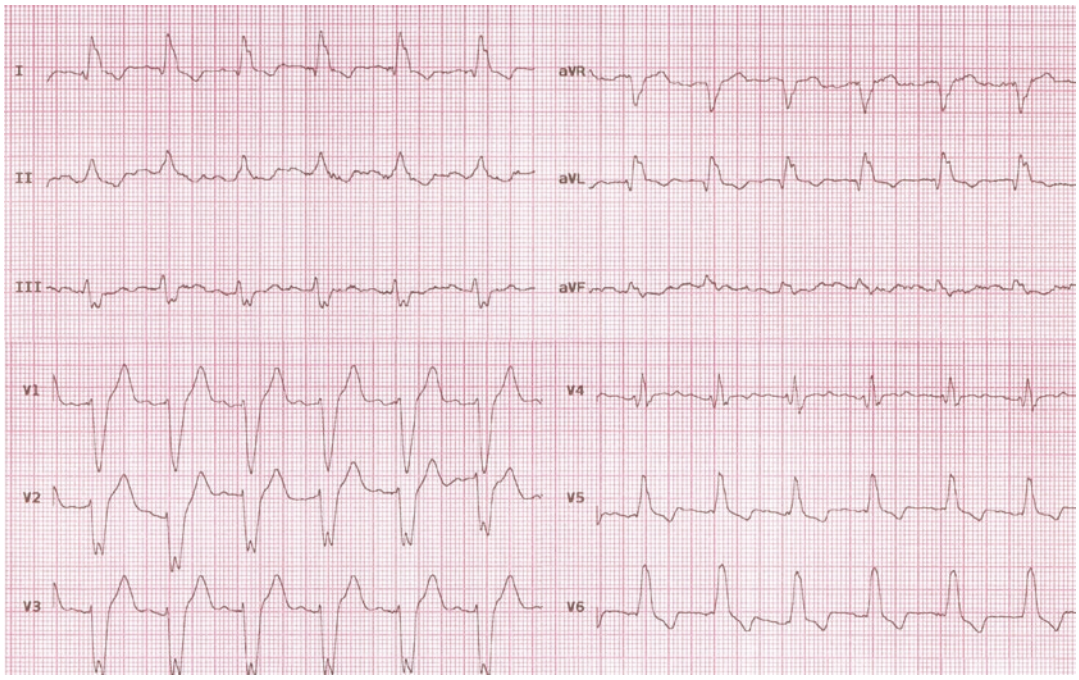

Fig. 12 Left bundle branch block. Typical features are absent q-wave in leads V5 and V6, notched slurred R in leads I, aVL, V5, and V6, broad S-wave in leads V1 and V2, ST depression with inverted T-wave in left precordial leads

fascicles of the His-Purkinje system. Bifascicular block is defined as the complete LBBB or the combination of RBBB with either LAFB or LPFB. Most cases were seen after the tetralogy of Fallot repair.

Trifascicular block is an electrical disorder in all three fascicles of the conduction system. This abnormality is diagnosed by the presence of alternating bundle branch block (alternating RBBB and LBBB or RBBB with alternating LAHB or LPHB). The bifascicular block with first-degree atrioventricular (AV) block is not necessarily indicative of trifascicular block because PR prolongation is related to the AV nodal disease in the majority of the cases.

Cardiac Tachyarrhythmias

Supraventricular Tachycardias

Supraventricular tachycardias (SVT) are a common problem in children who are presenting in the emergency department. In addition to cardiac arrhythmia, a fast heart rate can be a physiological response to pain, dehydration, and fever. SVT is the most common tachycardia in pediatric patients. It occurs with a frequency of 1 in 250 to 1 in 1000. Clinical presentation varies from poor feeding or lethargy in infants to palpitation, dyspnea, dizziness, and chest pain in older children.

Several mechanisms are responsible for SVT in children. Different types of pediatric SVTs are listed in Table 6. The most common type of pediatric SVT is orthodromic atrioventricular reciprocating tachycardia (AVRT) using an accessory pathway. Characteristic ECG findings for orthodromic AVRT (Fig. 13) are the presence of P-wave in the ST-segment during tachycardia

Table 6 Supraventricular tachycardias in children.

Sinus tachycardia (ST)
Orthodromic atrioventricular reciprocating tachycardia (O-AVRT)
Permanent form of junctional reciprocating tachycardia (PJRT)
Antidromic reciprocating tachycardia (A-AVRT)
Atrioventricular nodal reentrant tachycardia (AVNRT)
Junctional ectopic tachycardia (JET)
Focal atrial tachycardia (FAT)
Multifocal atrial tachycardia (MAT)
Atrial flutter (AFL)
Atrial fibrillation (AF)

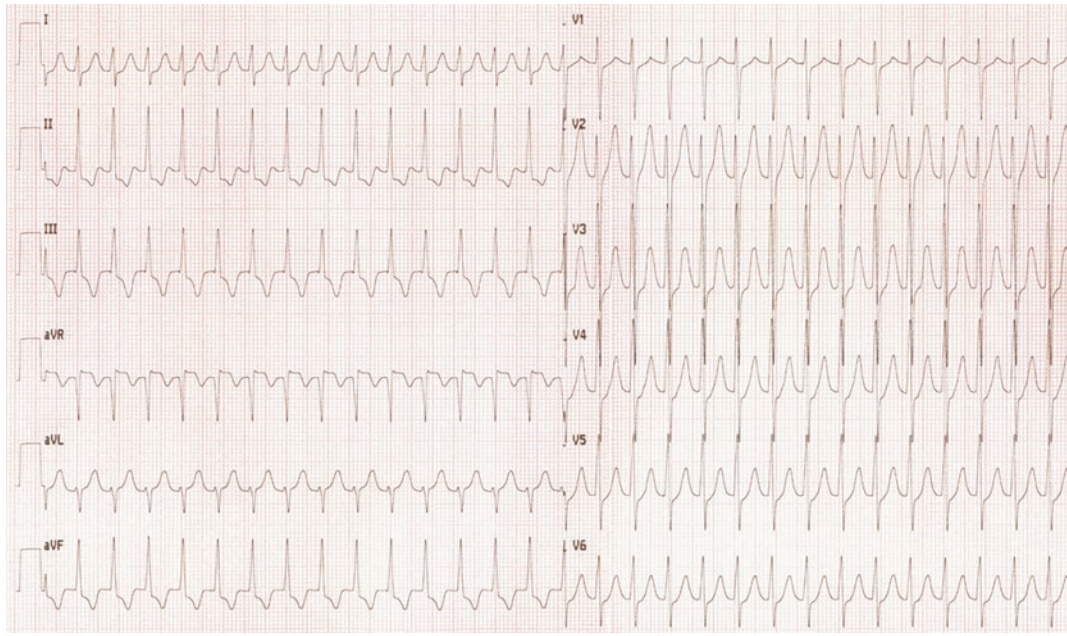

Fig. 13 Orthodromic atrioventricular reciprocating tachycardia. Note that there marked ST-segment depression in inferior and left precordial leads and ST-segment elevation in lead aVR

(QRS-P interval > 0.07 s), ST-segment depression in inferior and left precordial leads, ST-segment elevation in lead aVR, and Wolf-Parkinson-White pattern (short PR, wide QRS complex, and delta wave) in NSR (Fig. 14). The heart rate is typically more than 220 beats/min (bpm) in infants and more than 180 bpm in children.

Ventricular Tachycardias

Although pediatric tachycardias are more likely to be from a supraventricular origin, tachycardias from a ventricular origin do occur. Ventricular tachycardia (VT) usually presents with wide QRS tachycardia in ECG (Fig. 15). It is important to note that QRS complex duration is shorter in children than the adult, therefore, a tachycardia with slightly prolonged QRS may represent a VT or SVT with aberrancy. VT can go unrecognized for a while before presenting with syncope, heart failure, or cardiac arrest.

In surface ECG, VT is characterized by a series of three or more repetitive ventricular extrasystole with a heart rate of >120 bpm. It is highly important to remember the age-related QRS complex duration changes in children. In infants, the QRS complex duration in VT is more than 0.08 s, and in children older than 3 years is more than 0.09 s. Therefore, it is highly likely to misdiagnose the VT as SVT. To ensure proper diagnosis of VT, other useful criteria such as AV dissociation, capture, and fusion beats should be considered in these situations.

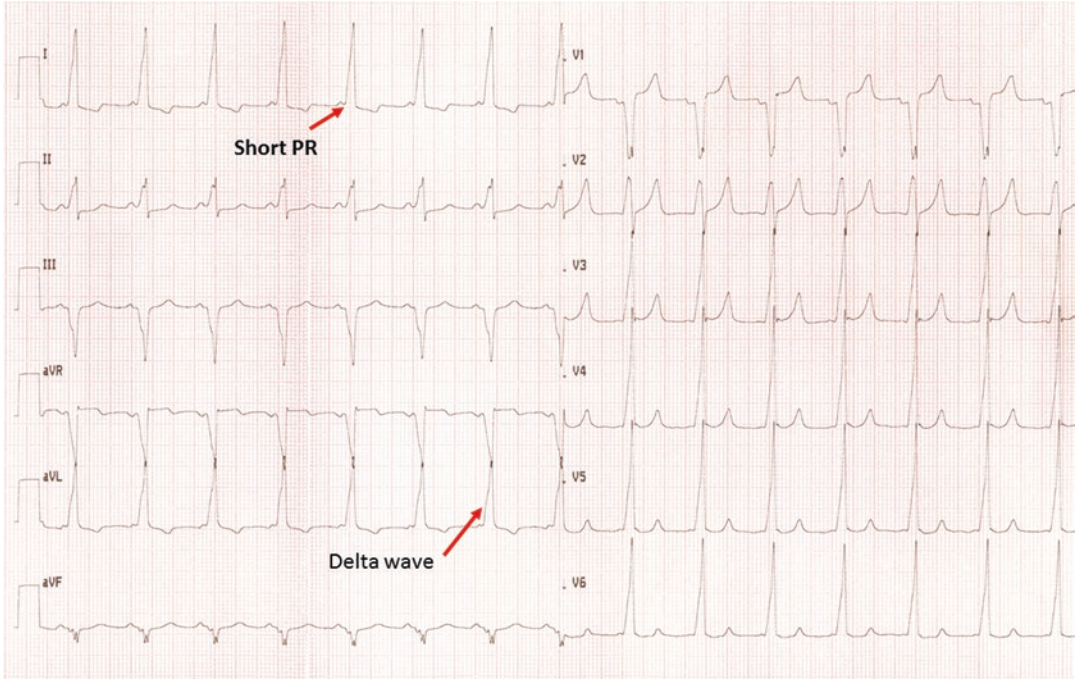

Fig. 14 Wolf-Parkinson-White syndrome. Characteristic features are short PR interval, delta wave (initial slurring of QRS complex), and QRS widening

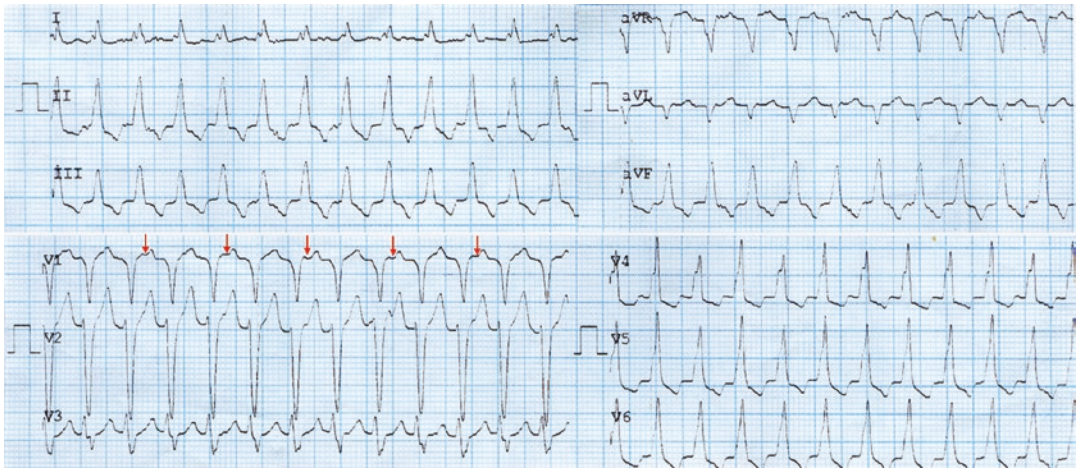

Fig. 15 Ventricular tachycardia. This ECG shows a wide QRS tachycardia with 2 to 1 ventriculoatrial association (red arrow)

Congenital Heart Disease

Atrial Septal Defect

Atrial septal defect (ASD) is a congenital heart disease with the left to right shunt. The ECG pattern mainly results from volume overload that is related to ASD size: in small ASD, ECG is usually normal, however, in the larger ASD, there is rsR' pattern in right precordial leads including V4R and V1 due to volume overload and RV conduction delay (Fig. 16). This ECG finding may be helpful in asymptomatic children as a clue for further evaluation for ASD but also may be observed in normal children. The P-wave axis is usually between 90 and 120 degrees (Zufelt et al. 1998). Frontal right axis deviation is observed in medium and large ASD (Fig. 16). The other types of ASDs have appropriate ECG findings. In sinus venosus ASD, the P wave axis may be less than 30 degrees or in ASD primum, the frontal left axis deviation is seen (Davia et al. 1973).

Ventricular Septal Defect

ECG findings in VSD determine based on the VSD size and degree of interventricular shunts. Because of limited left to right shunt in small VSD, ECG is normal or minimal change is seen. In moderate and large size VSD, left to right shunt degree is significant. Volume overload causes dilation and hypertrophy of LA and LV. The frontal axis deviates to the left and counterclockwise rotation occurred. LA enlargement causes a broad notched P wave in lead II (Fig. 17). A characteristic finding of large VSD is the sign of RVH on ECG. Latter findings become more prominent with an increase in pulmonary vascular resistance.

In neonate and infants with large VSD, an excessive amount of blood flow to pulmonary circulation prevents the natural decrease in pulmonary vascular resistance to occur in the first months of life. As a result, RV dominancy and RVH continue beyond the neonatal period. Patients with pulmonary vascular obstructive disease initially demonstrate biventricular hypertrophy (Fig. 17) and gradually progress to RVH only.

Atrioventricular Septal Defect

Failure of the endocardial cushion development to complete atrial and ventricular septation results in an atrioventricular septal defect (AVSD). The complete form of AVSD is characterized by ASD premium and inlet VSD. The AV node displaces from its normal position in the Koch triangle in the posteroinferior direction. The bundle has a

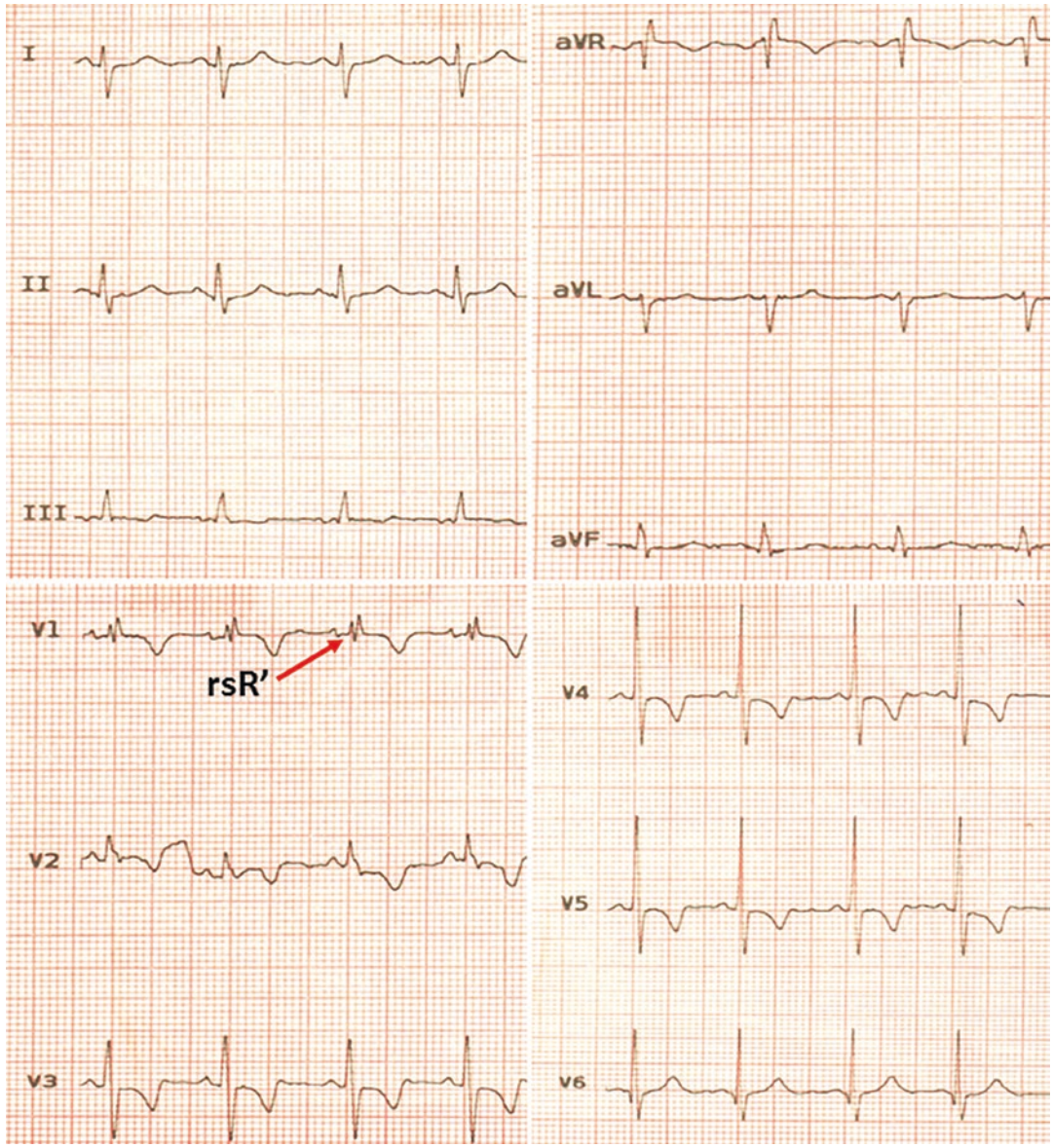

Fig. 16 Atrial septal defect. The rsR' pattern in lead V1 and right axis deviation are typical characteristics

longer course and descends along the crest of the ventricular septum. The superior axis deviation is one of the main ECG features of the AVSD (Fig. 18) and the axis is between −40 and −150 (Gamboa et al. 1966). The intra-atrial conduction delay results in PR prolongation. The RVH pattern in ECG is a constant finding (Fig. 18). LVH may also be observed.

In partial AVSD, the left axis deviation is observed and the frontal axis usually is between −30 and −150 degrees. The PR prolongation may be seen in about 50% due to increased intra-atrial conduction time (Park 2014). Other ECG findings include: RVH pattern, rsR in right precordial leads, RBBB, tall or broad, and notched P wave due to RA or LA enlargement.

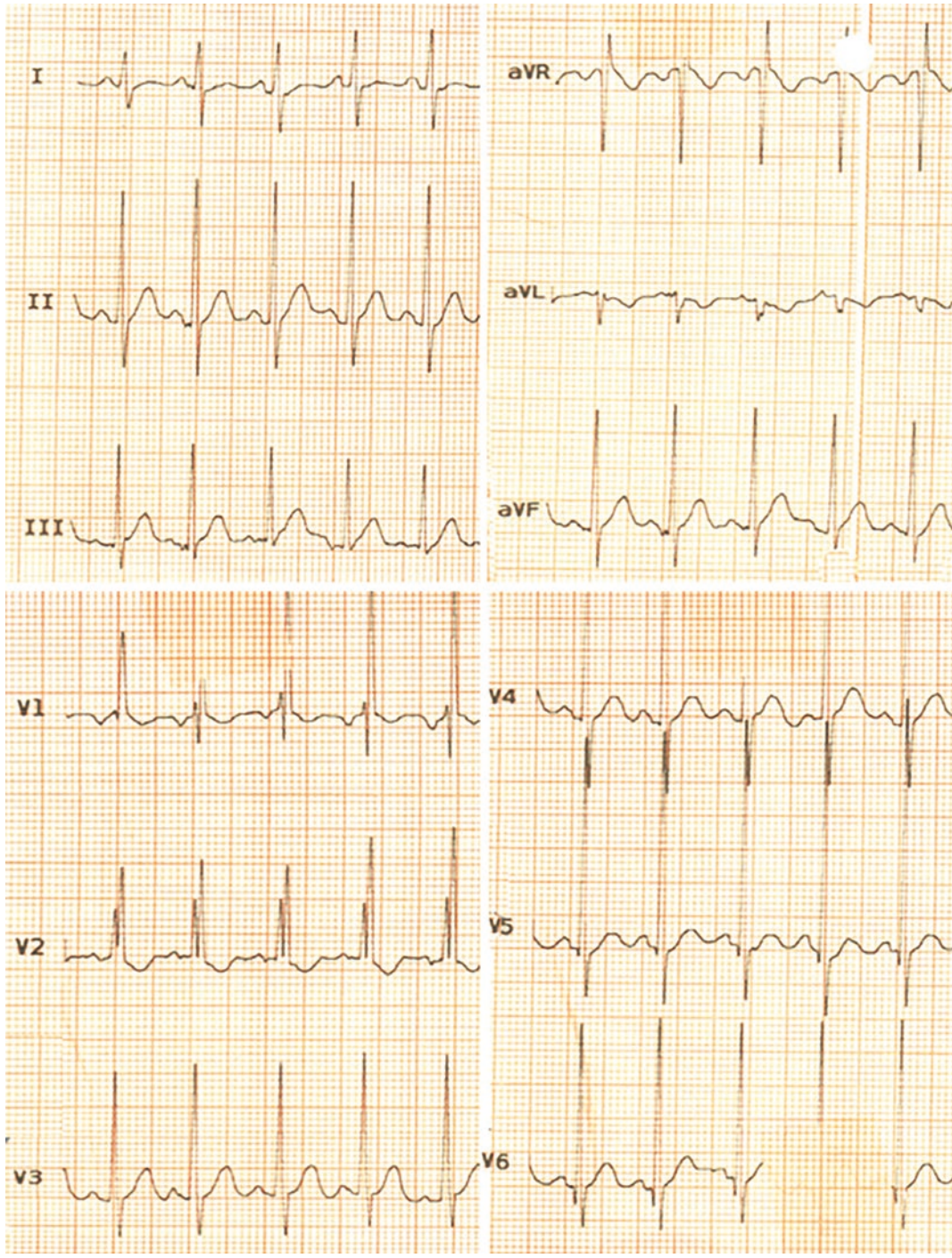

Fig. 17 Ventricular septal defect with pulmonary vascular disease. This ECG shows biventricular hypertrophy and left atrial abnormality

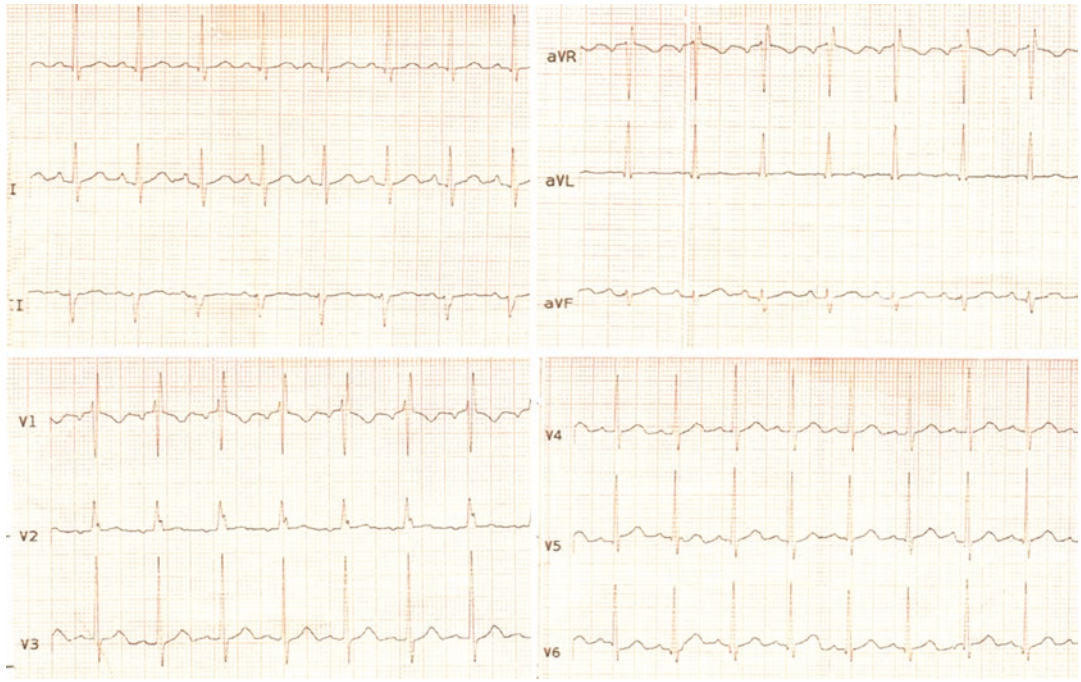

Fig. 18 Complete atrioventricular septal defect. Note that there is left axis deviation, incomplete right bundle branch block, and biventricular hypertrophy

Patent Ductus Arteriosus

The patent ductus arteriosus (PDA) has slightly different appearances in preterm and full-term neonates. In the preterm infant, lung disease causes the persistence of RV dominancy and the ECG may be confusing. Similar to other congenital heart diseases with the left to right shunt, left to right shunt, and severity of LV volume overload determines ECG pattern. In moderate-sized and large PDA, the ECG pattern of LVH is manifested by tall R wave and deep Q wave in inferior leads and leads V5-V6 (Fig. 19). There is also an LA abnormality with a broad biphasic P wave. Without intervention and the resulting increase in pulmonary pressure, ECG patterns of RVH and RA enlargement will have appeared.

Truncus Arteriosus

In truncus arteriosus , a single great artery with a single semilunar valve arises from the heart and this artery is the origin of the aorta, pulmonary, and coronary arteries. The ventricular septal defect is a constant finding. The baseline rhythm is normal sinus was usually because the AV node is located in a normal position. Similar to other congenital heart diseases with the left to right shunt, there is an ECG pattern of LVH and LA enlargement. Gradually, the BVH pattern may be seen.

Partially and Totally Anomalous Pulmonary Venous Returns

Total anomalous pulmonary venous return or TAPVC manifested with anomalous drainage of pulmonary vein to the right atrium or any pathway that terminated to RA. As a result, a huge blood volume loads to the right heart that increasing pulmonary blood flow. Severe RA and RV enlargement and RVH present. The ECG finding includes a frontal prominent R-wave in right precordial leads, upright T-wave in leads V4R and V1, and tall P wave in lead II.

In TAPVC with obstruction, ECG shows RVH and the right axis deviation because of pulmonary

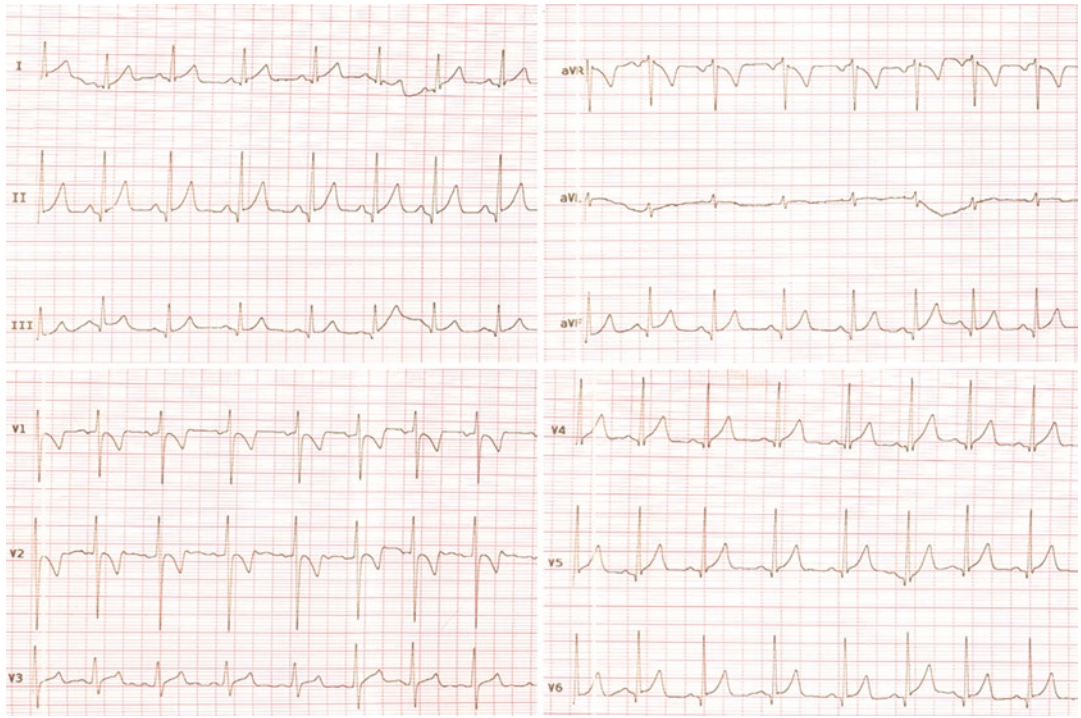

Fig. 19 Patent ductus arteriosus. There is typical left ventricular hypertrophy pattern with tall R wave and deep Q wave in inferior leads and leads V5-V6 and left atrial abnormality

hypertension. The ECG finding of partial anomalous pulmonary venous return (anomalous connection of one to three pulmonary veins) with ASD resembles isolated ASD. In PAPVC with the intact ventricular septum, ECG is normal.

Tricuspid Atresia

Tricuspid atresia is classified based on the position of great arteries and the presence of VSD. The AV node is located in the muscular floor of the right atrium and the bundle of His descends along the posterior rim of the VSD is near to the acute cardiac margin. As opposed to other cyanotic congenital heart diseases, the frontal axis deviates to the left superior because of decreased RV dominancy. The ECG sign of RA enlargement appeared a few months after birth.

In patients with large VSD and increased pulmonary blood flow, a tall R-wave and deep Q-wave in the left precordial lead were seen (Gamboa et al. 1966). Chronic RA stretching predisposes the heart to atrial arrhythmias such as atrial tachycardia and flutter.

Pulmonary Valve Stenosis and Pulmonary Valve Atresia

Based on the severity of RV outlet obstruction, the spectrum of disorders from mild valvular stenosis to severe pulmonary atresia with RV hypoplasia is observed. In mild pulmonary valve stenosis, ECG may be normal, but in moderate and severe stenosis right axis deviation and RVH are usually seen (Fig. 20). One practical formula for calculation of RV systolic pressure in presence of pure R-wave in V1 is (Dic et al. 1975): RV systolic pressure (mmHg) = R wave height (mm) × 5.

In severe form, the frontal axis is more than 110 degrees. Other ECG findings include RBBB, QR wave in right precordial leads. If there is the

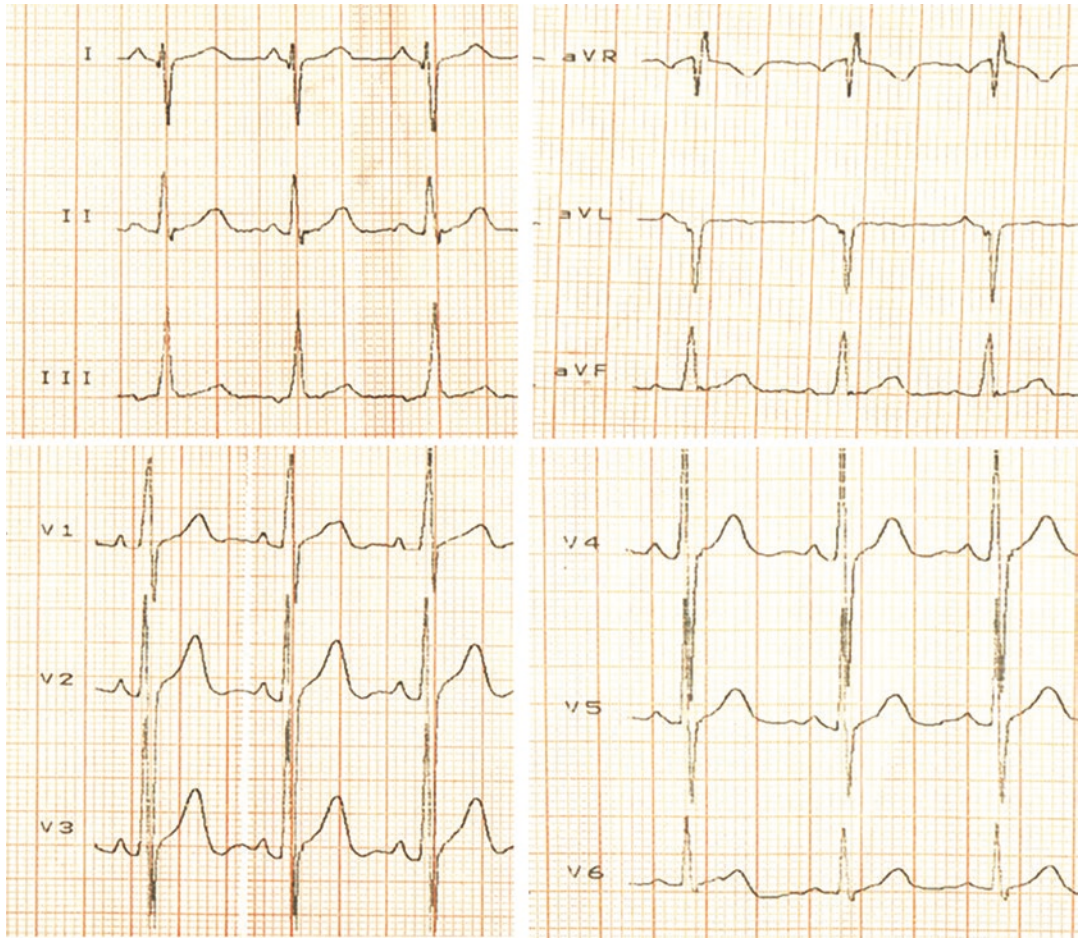

Fig. 20 Pulmonary valve stenosis. ECG shows right atrial abnormality (lead V1), right axis deviation, and right ventricular hypertrophy pattern

left axis deviation and LVH in critical PS, more evaluation for the diagnosis of Noonan syndrome is recommended.

Pulmonary atresia with intact ventricular septum results in underdevelopment and hypoplasia of RV. As opposed to other cyanotic heart diseases, the right and anterior forces are decreased. Neonate with LVH findings on ECG and significant cyanosis raises the suspicion of diagnosis the pulmonary atresia and intact ventricular septum. The ASD or PFO is always present and ECG shows RA enlargement. Due to coronary arteries involvement and ventriculocoronary connections, ischemic patterns of ST-T changes may be seen in these patients.

In presence of the VSD, RV pressure overloads occurred and ECG shows right axis deviation and RVH. In rare cases that multiple and large collaterals result in increased pulmonary blood flow, LVH and LA enlargement are seen in ECG.

Tetralogy of Fallot

Deviation of the infundibular septum in the fetal period begins the complex pathology of TOF. This anomaly includes pulmonary stenosis and VSD that results in right axis deviation and RVH in ECG. The SA node and AV node are intact but cases of complete AV block were seen.

After conventional surgical repair, one of the well-known ECG patterns is RBBB (Fig. 21). Association of RBBB with left anterior fascicular block may also have occurred. The effects of the pulmonary valve insufficiency (PI) in a long period on RV remodeling and LV function necessitate a regular evaluation of PI severity after surgery. The length of the QRS complex is one of the markers that predict the severity of pulmonary insufficiency, the needs for pulmonary valve replacement, and adverse outcome. The QRS duration equal to or more than 180 ms predisposes these patients to ventricular tachyarrhythmia. In multicenter studies on 800 patients with TOF, the QRS duration equal to or more than 180 ms or more than 5 ms annual increase in the QRS duration was a predictor for sudden cardiac death (Gatzoulis et al. 1995). Progressive ventricular fibrosis and dilation are the natural course of TOF and unoperated older age patients exhibit ventricular ectopy. The SVT including atrial arrhythmias, atrial flutter, and fibrillation have also been reported after total correction in long-term follow-up.

Ebstein Anomaly

Ebstein's anomaly is characterized by some degree of tricuspid valve displacement toward the RV cavity. The addition of atrialized RV to the RA chamber changes the electroanatomical map of the right atrium. The intra-atrial conduction delay results in PR prolongation in approximately 40% of patients. The RA enlargement and tricuspid valve regurgitation result in a tall peaked P wave in ECG especially lead II and an increase in the duration of P-wave. Other ECG findings include RBBB and Q-wave in right precordial leads. The disruption of the atrioventricular fibrosis tissue that separates the atrium from the ventricles electrically predisposes this anomaly to muscle bridge connections termed

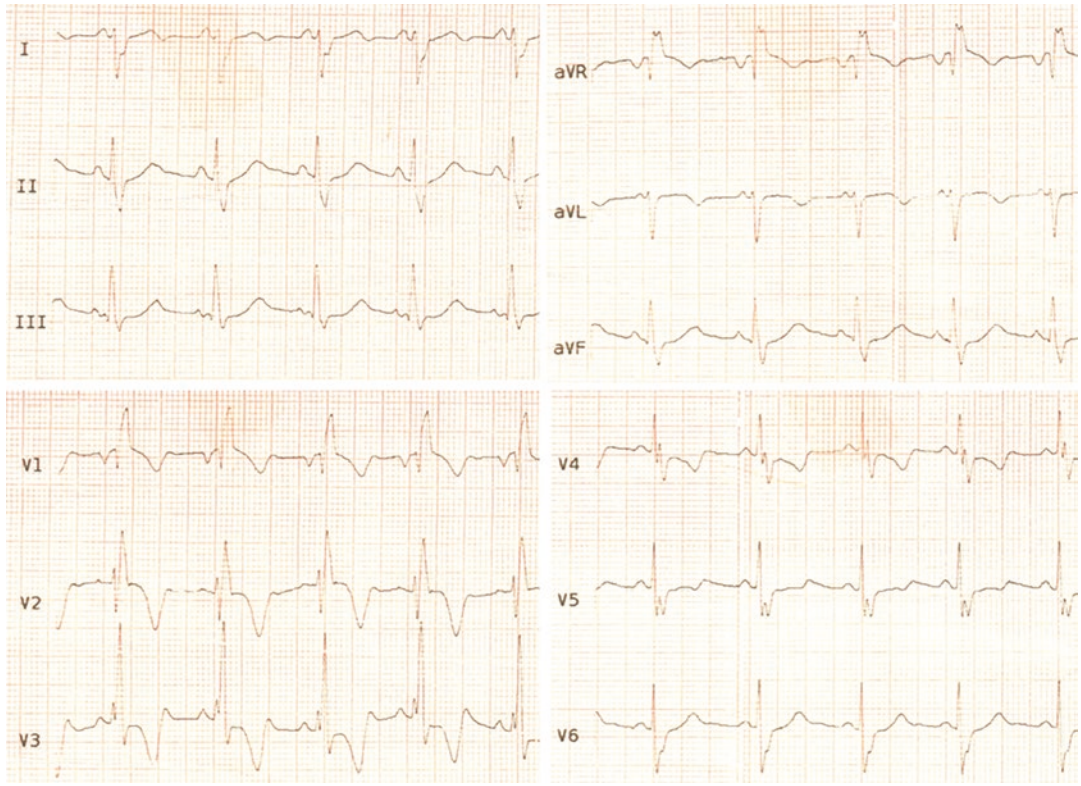

Fig. 21 Tetralogy of Fallot after surgical repair. Typical sign is right bundle branch block

accessory pathways. These pathways bypass the normal conduction system and result in preexcitation and WPW syndrome.

Cappato and coworkers studied 21 patients with Ebstein's anomaly and AV reciprocating tachycardia. All accessory pathways were right-sided typically in the posteroseptal, posterior, and posterolateral positions (Cappato et al. 1996). Multiple accessory pathways have been reported in 6–36% of patients with WPW syndrome. Reich et al. investigated 59 patients with Ebstein's anomaly and AP-mediated arrhythmias (Reich- et al. 1998). They found multiple accessory pathways in 33% of pathways and 96% of pathways were right sided.

In Ebstein's anomaly, other tachyarrhythmias are also common. These arrhythmias include atrial tachycardia, atrial flutter, atrial fibrillation, and ventricular tachycardia. The SVT in the presence of rapid conducting accessory pathways could deteriorate the unstable hemodynamic state of patients with severe Ebstein's anomaly. Radiofrequency ablation for the elimination of all accessory pathways is recommended before corrective surgery of the tricuspid valve, however, the recurrence rate is high.

Aortic Valve Stenosis

Such as other left-sided obstructive diseases, aortic valve stenosis presents with pressure overload and LVH. Both voltage and repolarization criteria in ECG are useful for identifying the LVH. With progression to severe stenosis, the sign of subendocardial ischemia and strain pattern as inverted T-wave and ST-segment depression in left precordial leads appear. Even in severe aortic valve stenosis, the resting ECG may be normal and appropriate tests include exercise tests and 24-h ECG Holter monitoring. During the exercise test, significant ST-segment changes were observed in the severe form of the disease.

Wagner et al. reported that patients with severe AS (peak to peak pressure gradient more than 80 mmHg) did not present with ECG findings on ECG and T-wave morphology in lead V6 was only discriminatory ECG finding in 2 to 21-year-old patients (Wagner et al. 1977). Wolf et al. reported that the prevalence of ventricular ectopy and ventricular arrhythmias is higher in 24-h Holter monitoring of patients with aortic valve stenosis (Wolfe et al. 1993).

Coarctation of the Aorta

The COA is usually present in adolescence with systemic hypertension. The ECG finding of LVH is usual and LA abnormality is also observed in chronic untreated COA (Fig. 7). In neonate and infancy, the COA is asymptomatic and ECG is usually normal. It is important to note that the presence of LVH in this period necessitates ruling out other left-sided obstructive diseases including aortic valve stenosis.

Transposition of the Great Arteries

In TGA, aorta origin arises from morphological RV and pulmonary artery origin arises from morphological LV. Therefore, there is parallel circulation, and the desaturated venous blood returns to the systemic circulation, and saturated pulmonary venous blood returns to the pulmonary artery. In the neonatal period, the RV pressure is normally high and after this period with reducing pulmonary vascular resistance gradually decreased to normal value. In TGA, the RV should pump blood against systemic circulation and the ECG finding of RVH is present after the first week along with right axis deviation (Fig. 22). In presence of the VSD, biventricular hypertrophy is observed.

The typical ECG finding of TGA maybe not be found in the presence of other anomalies such as pulmonary stenosis or atrioventricular septal defect.

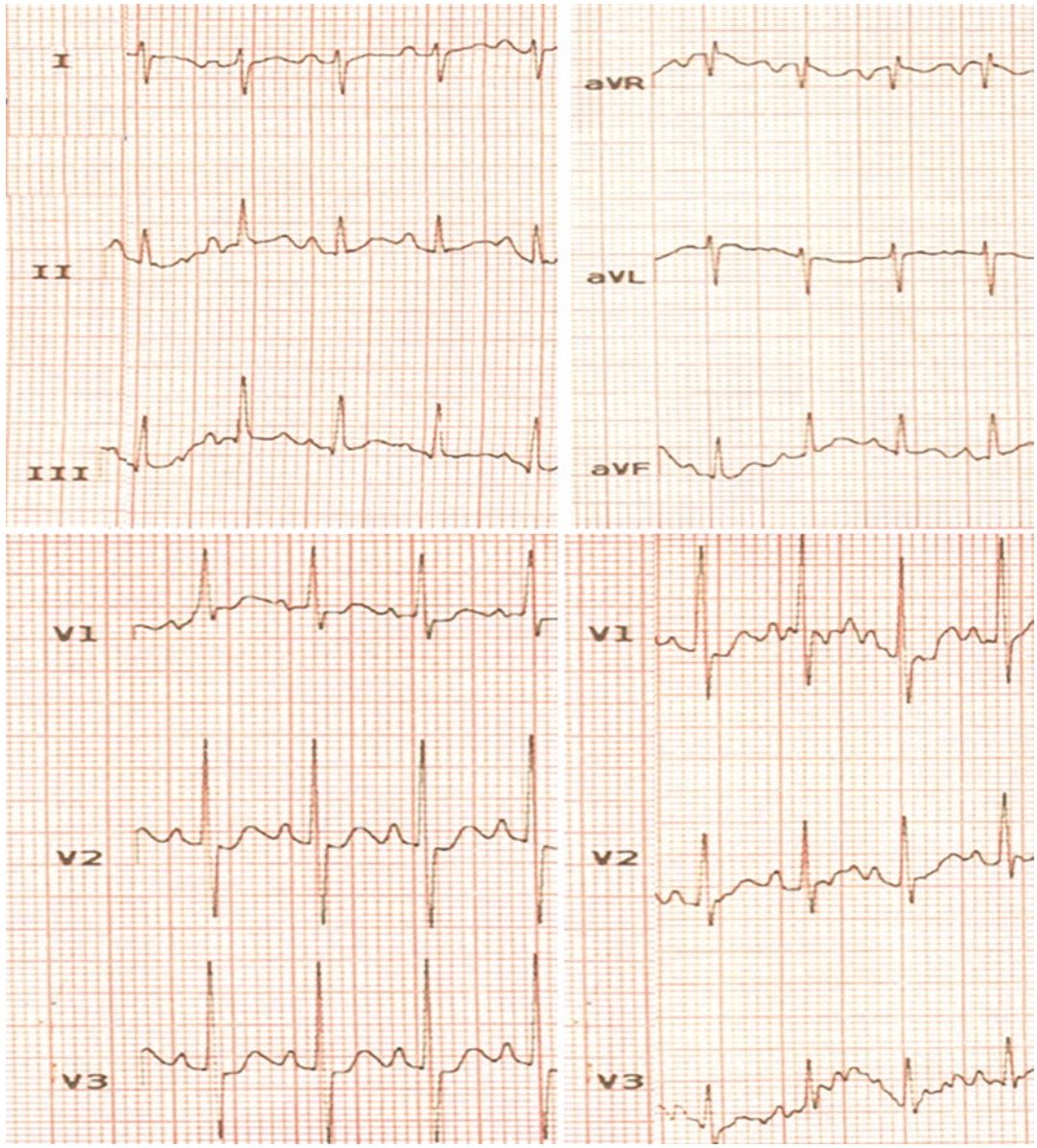

Fig. 22 Transposition of great arteries. This ECG shows right axis deviation and right ventricular hypertrophy pattern.

Congenitally Corrected Transposition of the Great Arteries

In congenitally corrected transposition of the great arteries (CCTGA), the right-sided and anterosuperior ventricle has LV morphology and the left-sided and posteroinferior ventricle has RV morphology but the atria and great arteries connect normally with inverted ventricles. This atrioventricular and ventriculoarterial discordance results in normal circulation physiology, but there are conduction system disorders and associated structural diseases because of improper roles of LV and RV.

In CCTGA, the SA node is inserted in the SVC-RA junction in a normal position and the

atrial conduction is direct from the right and anterior to left and posterior, therefore the P wave axis and morphology are normal. The main factor that determines the AV node location is the presence or absence of atrioventricular concordance. In CCTGA, the AV node is located in the RA wall and anterosuperior quadrant of the mitral valve. The bundle runs between the mitral valve and valve of the posterior great artery and descends anterior to the outflow tract of the posterior great artery. In the presence of the VSD, the location of the nonbranching bundle to the VSD is anterosuperior. The left bundle descends on the right side of the interventricular septum and the right bundle penetrates the septum and shifts to left (Ho and Anderson 1985).

In a normal structural heart, the initiation of ventricular depolarization is from left to right of the interventricular septum. Because the mean frontal conduction axis is away from the left and inferior precordial leads, the initial QRS force is negative and Q waves in leads V5 and V6 are observed. In CCTGA, the initial depolarization direction reversed because of inverted left and right bundle branches. The ECG finding includes: Absence of Q wave in leads V5, V6, and presence of QS complex in leads V4R and V1, large Q wave in leads III and aVF, left axis deviation, and first-degree AV block present in 50% of patients.

The CCTGA can also present with a complete AV block. Complete AV block occurs in 4% of newborns with CCTGA that may be progressive and lifetime incidence is 20 to 30% (Huhta et al. 1983). CCTGA is also on the top list of postsurgical complete AV blocks. The presence of accessory pathways and WPW syndrome is more common in CCTGA.

Cardiomyopathy

Hypertrophic Cardiomyopathy

Hypertrophic cardiomyopathy (HCM) is characterized by LVH without any obvious cause. The ECG patterns of HCM are nonspecific. The voltage criteria of LVH including tall R-wave in left precordial leads and deep S-wave in right precordial leads are usually observed (Fig. 23). The ST-T changes and LA enlargement are other ECG findings. These criteria did not correlate well with the severity of LVH and LV outflow tract obstruction.

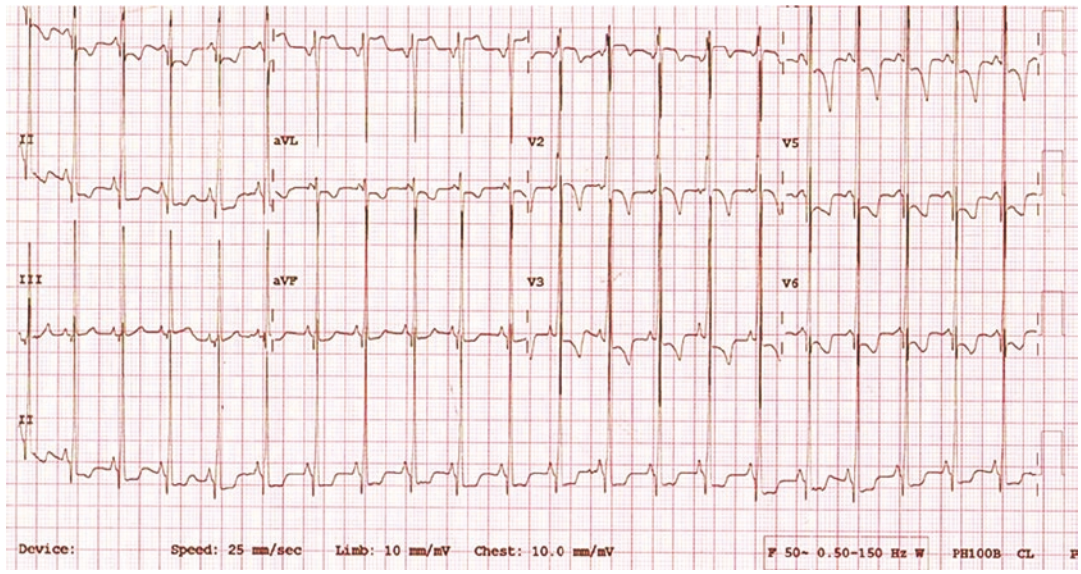

Fig. 23 Hypertrophic cardiomyopathy in a patient with Pompe disease. Note that there are tall R-wave in left precordial leads and deep S-wave in right precordial leads

With the progression of the disease, the ischemic ECG pattern as deep Q-wave in inferior and left lateral precordial leads appears. Interestingly, the ECG pattern of RVH may be seen in an infant with HCM. In the presence of giant negative T-waves in left precordial leads, apical HCM should be considered.

Chronic pressure overload on the ischemic LV myocardium predisposes the patient to ventricular tachyarrhythmia and ectopy. Pre-excitation is reported in some form of HCM with a genetic basis. In addition, other supraventricular tachyarrhythmias, including atrial tachycardia, atrial flutter, and atrial fibrillation have been reported.

Dilated Cardiomyopathy

The DCM is the primary myocardial involvement with dilatation of LA and LV. In DCM, ECG shows LVH and LA enlargement. The nonspecific ST-T changes were seen. Several types of supraventricular and ventricular arrhythmias are seen in DCM and ventricular arrhythmia is one of the main causes of death.

Arrhythmogenic Right Ventricular Cardiomyopathy/Dysplasia

Arrhythmogenic right ventricular cardiomyopathy/dysplasia (ARVC/D) is a genetic disorder with fibrofatty replacement of the myocardial tissue that involves mainly the right ventricle. The disease is usually inherited as autosomal dominant.

ECG usually shows depolarization and repolarization abnormalities. These patients may be present with ventricular arrhythmia, syncope, and sudden cardiac death. Epsilon wave (any deflection between the end of the QRS complex and onset of T-wave in leads V1-V3) is the characteristic ECG finding on ECG (Fig. 24) (Marcus et al.

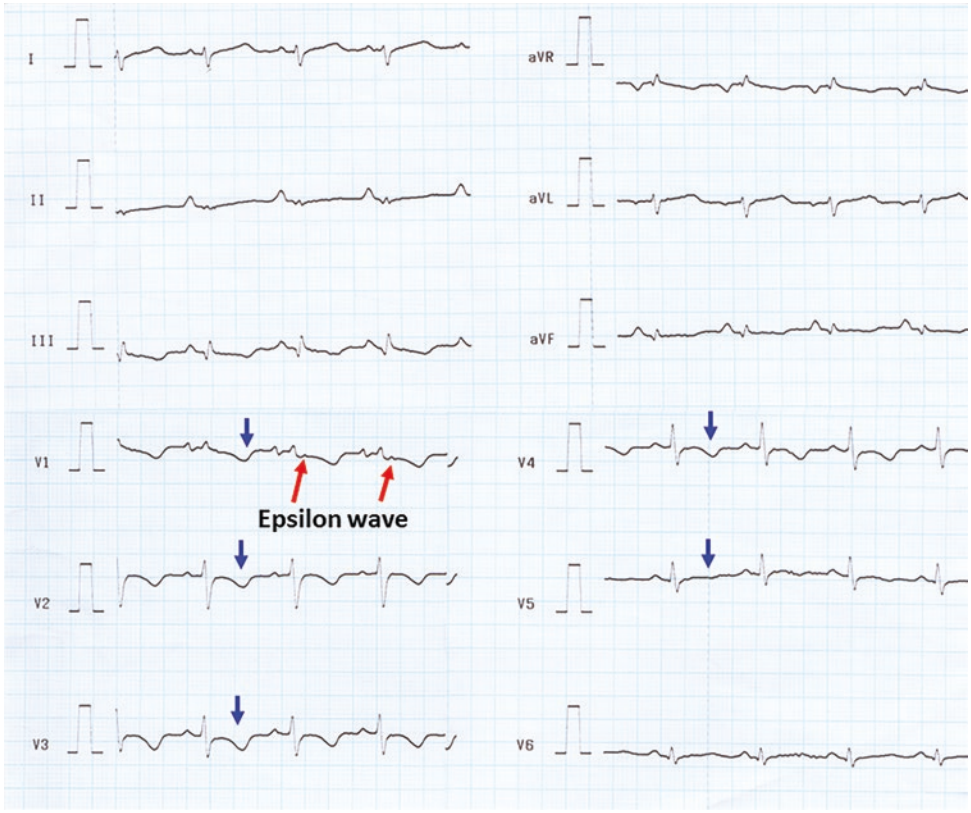

Fig. 24 Arrhythmogenic right ventricular cardiomyopathy/dysplasia. Pathognomonic signs are epsilon waves (red arrows) and T wave inversion in leads V1-V3 and beyond

2010). Epsilon wave is more common in children than the adult. Isolated wide QRS complexes in right precordial leads and T-wave inversion in leads V1-V3 and beyond are other characteristic findings, however, negative T-wave in leads V1, V2 may be a normal variant in children.

Due to the progressive nature of myocardium disease, ventricular arrhythmias are more common in ARVD/C and may be life-threatening. VT usually has a left bundle branch block pattern but other forms such as polymorphic VT and VF are also observed.

Restrictive Cardiomyopathy

The RCM is a myocardial disease that is characterized by restricted ventricular filling. Severe biatrial enlargement with small-sized ventricles is typical echocardiographic findings. The constant ECG findings are LA enlargement, RA enlargement, or both. Other ECG finding includes LVH, RVH, ST-T changes, and ST-segment depression.

Due to the nature of the RCM, arrhythmias are common. Atrial flutter is the most common type of arrhythmia in these patients. Other types of atrial arrhythmias are also observed. AV block is also reported especially in familial RCM (Fitzpatrick et al. 1990; Walsh et al. 2012).

Dystrophies

Duchenne Muscular Dystrophy

In Duchenne muscular dystrophy (DMD), progressive myocardial fibrosis results in severe heart failure. ECG finding includes short PR interval, deep Q-waves in lateral and left precordial leads, and RVH pattern (Perloff et al. 1967). A prolonged QT interval was reported in some patients. Supraventricular and ventricular arrhythmia is common in the end-stage of disease. Becker muscular dystrophy is another dystrophinopathy that has a slower progressive pattern and ECG finding is similar to DMD.

Myotonic Muscular Dystrophy

Myotonic muscular dystrophy (MMD) is the most common type of muscular dystrophy with autosomal dominant inheritance (Pelargonio et al. 2002). In contrast to other muscular dystrophies, MMD is manifested by progressive conduction system abnormalities. Therefore, different types of conduction abnormalities, including first-degree AV block, second-and third-degree AV block, and wide QRS may be observed.

These patients have a slower rate in comparison to other normal children. The QT interval is prolonged and predisposes patients to Torsades de pointes. Ventricular arrhythmia, atrial flutter, and atrial fibrillation may occur in this disorder (Facenda-Lorenzoa et al. 2013).

Inflammatory Conditions

Kawasaki Disease

Kawasaki disease is an autoimmune heart disease that is characterized by coronary vasculitis and may result in aneurysm formation, thrombosis, and myocardial infarction.

In the acute phase, ECG finding of myocarditis is usually observed. Low voltage QRS complexes, ST-T changes, and sinus tachycardia may occur. Aneurysmal formation in the coronary artery may lead to thrombosis and myocardial infarction. The posterior wall myocardial infarction occurred following RCA involvement that was characterized by deep Q-waves and ST-segment elevation in inferior leads (Surnitorno et al. 2008).

Pericarditis

Pericarditis is an inflammatory disease of the pericardium. Pericarditis is the most common cause of ST elevation in children. ECG is a useful tool for the evaluation of pericarditis. In pericarditis, ECG changes are usually classified into four stages:

1. *Stage 1*: ST-segment elevation appears in almost all leads, especially lateral and inferior leads with PR interval depression.
2. *Stage 2*: ST- and PR-segment returns to normal baseline.
3. *Stage 3*: diffuse T wave inversion.
4. *Stage 4*: ECG returns to normal usually 2 to 4 weeks after onset of disease.

Massive pericardial effusion with low voltage QRS and QRS alternans are other ECG findings in pericarditis. QRS alternans are defined as a periodic change in QRS amplitude.

Myocarditis

Myocarditis is an inflammatory myocardial process that is terminated in myocardial necrosis. The primary change in ECG is sinus tachycardia. The low voltage QRS complex and ST-T changes are seen due to diffuse damage to the myocardium. The PR prolongation and increased QT interval may be seen. Q-waves indicate acute myocardial necrosis. The myocardium inflammation predisposes these patients to several ventricular and supraventricular arrhythmias.

Acute Rheumatic Fever

Acute rheumatic fever (ARF) is a cardiac inflammatory process following pharyngeal streptococcus infection. PR interval prolongation is one of the well-known diagnostic criteria for ARF.

In chronic rheumatic heart disease with mild valvulitis, the ECG usually will be normal. The ECG finding in chronic mitral regurgitation shows LA enlargement and LVH. LA enlargement will be significant in mitral stenosis and also RVH gradually appeared. Atrial enlargement is a substrate for supraventricular arrhythmia. The aortic valve is the second common valve involved in ARF. Aortic regurgitation manifested with LVH on ECG.

Cardiac Tumors

Rhabdomyoma

Rhabdomyoma is the most common type of cardiac tumor in children. The ECG pattern depends on the size of the tumor and its proximity to the conduction system. In large rhabdomyoma, ECG shows ventricular hypertrophy and ST-T changes. Conduction system compression by a tumor may produce AV block and bundle branch block.

Effects of tumor on hemodynamic condition and conduction system involvement predisposed these patients to supraventricular or ventricular tachyarrhythmias. Pre-excitation has also been reported. Rhabdomyomas may regress with time, therefore, pre-excitation and other arrhythmias may resolve spontaneously.

In some patients, ventricular arrhythmia may be sustained and resistance to drug therapy and radiofrequency catheter ablation. In this condition, tumor resection is the only definite way for treatment (Miyake et al. 2011).

Fibroma

Fibroma is the single intramural tumor most commonly found in the LV. The ECG pattern is similar to rhabdomyoma. Arrhythmia is usually presented as ventricular tachycardia that may be fatal in some cases (Miyake et al. 2011).

Myxoma

Myxoma is the single left atrium tumor that may be obstructing LV inflow. ECG showed LA enlargement and in large tumors, RVH gradually appeared because of pulmonary hypertension. Tumor embolization to the pulmonary artery also results in RVH pattern on ECG (Zitnik and Giuliani 1970).

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Central Nervous System Monitoring in Pediatric Cardiac Surgery

Ali Dabbagh and Michael A. E. Ramsay

Abstract

During the last decades, significant improvements have been gained in the general surgical outcome of congenital heart surgeries. However, we have to focus more on the overall clinical outcome, especially neurodevelopmental aspects. Postoperative neurologic complications have a great impact on outcome; being more frequent and much more serious in smaller age babies; usually, neonates are the most vulnerable group. The incidence of major central nervous system (CNS) lesions after congenital heart surgeries is not more than 10%; while the incidence of Postoperative Cognitive Impairments (POCI) may be as high as 50%. POCI in pediatric congenital heart disease (CHD) surgeries could be one or more of these three (Markowitz et al., Semin Cardiothorac Vasc Anesth 11:59–65, 2007; Ghanayem et al., J Thorac Cardiovasc Surg 140:857–863, 2010; Snookes et al., Pediatrics 125:e818–827, 2010; Heneghan and Pollack, Pediatr Clin N Am 64:1147–1165, 2017; Calderon et al., Arch Dis Child 103:49–56, 2018):

- cognitive dysfunction,
- impairments in the organization of motor functions,
- emotional and functional dysfunction.

This chapter reviews the main methods for monitoring CNS in the perioperative period, starting with clinical assessment of CNS status in children; then going to technologies including Near-Infrared Spectroscopy (NIRS), Electroencephalography (EEG), Transcranial Doppler (TCD), Jugular venous oxygen saturation (SjVO2), monitoring depth of anesthesia, and Evoked potentials. The final goal of this chapter is to introduce a range of methods to monitor CNS function in routine clinical practice in such a way that could be used for the prevention of unwanted structural or behavioral CNS lesions.

Keywords

Pediatric · Central nervous system · Monitoring · Congenital heart diseases · Pediatric cardiac surgery

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Introduction: Role of CNS Monitoring in Pediatric Cardiac Surgery

During the last decades, significant improvements have been gained in the general surgical outcome of congenital heart surgeries, especially in neonates and younger children. However, these improvements have led us to focus more on the clinical outcome of these patients, especially regarding neurodevelopmental indices. In fact, with improved surgical techniques, postoperative CNS outcome is one of the most important long-term concerns and one of the most important outcome surrogates for CHD surgeries. Postoperative neurologic complications could be potentially more frequent and much more serious as much as the age of surgery declines; usually, neonates are the most vulnerable patient group (Ghanayem et al. 2010; Snookes et al. 2010; Govers et al. 2014; CHT et al. 2015; Heneghan and Pollack 2017; Calderon et al. 2018).

On the other hand, among perioperative CNS injuries, nowadays we focus on impairments more than just seizures and focal lesions; while these are still considered significant. Reports have demonstrated the incidence of major CNS lesions after CHD surgeries is not more than 10%; while the incidence of cognitive impairments is up to 50%, based on the center and the duration of follow-up years (Markowitz et al. 2007; Ghanayem et al. 2010; Butler et al. 2017; Heneghan and Pollack 2017; Schunck et al. 2020).

Postoperative Cognitive Impairments (POCI) in pediatric CHD surgeries could be categorized into these sub-groups (Bellinger et al. 1997; Limperopoulos et al. 2001; Markowitz et al. 2007; Majnemer et al. 2008; Schunck et al. 2020):

- Cognitive dysfunction (including language impairments).
- Impairments in the organization of motor functions (including fine and gross motor impairments, visual-spatial dysfunction, etc.).
- Emotional health dysfunction and functional limitations include attention deficit disorder, behavioral impairments, internalizing problems, externalizing problems, functional limitations in socialization, impairments in daily living skills, defects in communication, and impairments in adaptive behavior.

Clinical Assessment of Pain and Sedation in the Postoperative Period in Children

Pediatric patient arousal state and responsiveness is always a clinical challenge. Many pediatric sedation assessment scales have been clinically used for many years; however, the core outcome measured by each of them is not the same.

When dealing with CNS, both the ***level of consciousness*** and the ***pain state*** are important.

Assessment of Pain

The reader is referred to the chapter dealing with *postoperative pain in pediatric cardiac anesthesia* in this book; however, a summary of the most commonly used scales is presented here. More than 20 observational ***pain scales*** have been assessed and reviewed in two systematic reviews (von Baeyer and Spagrud 2007; McGrath et al. 2008). Based on these studies and other similar ones, the following 5 scales are much more suitable for pediatric patients undergoing cardiac surgery:

The Children's Hospital of Eastern Ontario Pain Scale (CHEOPS)

1. Face, Legs, Activity, Cry, Consolability Scale (also Modified FLACC).
2. The COMFORT Scale.
3. Toddler Preschool Postoperative Pain Scale (TPPPS).
4. Parents' Postoperative Pain Measure (PPPM).

The Children's Hospital of Eastern Ontario Pain Scale: CHEOPS

First introduced in 1985 by McGrath et al., CHEOPS is an observational pain assessment tool for 1–7 years old children. This scale has

well-established reliability and validity. CHEOPS has 6 items scored 0–3 and the final score ranges from 4 to 13; with a final score of 4–6 denoting "no pain." The items assessed in CHEOPS are:

- Cry (1–3).
- Facial expression (1–3).
- Verbalization (0–2).
- The activity of torso (1–2).
- Touch (1–2).
- Response of legs (1–2).

The scale is more appropriate for "*postoperative pain*" assessment and "*procedural pain*" assessment (McGrath et al. 1985; Merkel et al. 1997; Hesselgard et al. 2007; von Baeyer and Spagrud 2007; McGrath et al. 2008).

Face, Legs, Activity, Cry, Consolability Scale (FLACC)

It was first described by Merkel et al. in 1997. FLACC is the acronym for ingredients of a pain assessment checklist. The items used in FLACC are much similar to CHEOPS but are designed in 0–10 metrics to make them easier to use. FLACC includes 5 items, each scoring 0–2 with a total score range of 0–10 with 0 representing no pain; it is applicable for children from 4 to 18 years old. Also, FLACC could be used in children with cognitive impairment. The items assessed in FLACC are:

- Face (0–2).
- Legs (0–2).
- Activity (0–2).
- Cry (0–2).
- Consolability (0–2).

FLACC has relatively fair reliability; but moderate validity and is appropriate for the assessment of "*postoperative pain in hospital*" and "*procedural pain*"; however, Crellin et al. questioned using FLACC in all circumstances and populations to which is currently applied (Merkel et al. 1997; Malviya et al. 2006; von Baeyer and Spagrud 2007; McGrath et al. 2008; Verghese and Hannallah 2010; Voepel-Lewis et al. 2010; Crellin et al. 2015).

COMFORT Scale

First described by Ambuel et al. in Ambuel et al. 1992, currently COMFORT is the only scale available for *children on a ventilator* or in a *critical care setting*. It is composed of 8 items; each item could be ranked 0–5 and the final score will be from a minimum of 8 up to a maximum of 40. Among the items, 2 of 8 are directly hemodynamic variables; the items assessed in COMFORT are:

- Alertness (1–5).
- Calmness/agitation (1–5).
- Respiratory response (1–5).
- Physical movement (1–5).
- Blood pressure (1–5).
- Herat rate (1–5).
- Muscle tone (1–5).
- Facial tension(1–5).

COMFORT is one of the best available scales for assessment of sedation in *mechanically ventilated* patients; especially in patients undergoing cardiac surgery. It has good reliability and internal consistency (Ambuel et al. 1992; Johansson and Kokinsky 2009; Lamas and Lopez-Herce 2010; Voepel-Lewis et al. 2010).

Toddler Preschool Postoperative Pain Scale (TPPPS)

TPPS was first described by Tarbell et al. in Tarbell et al. 1992, the scale is most applicable for children aged 1–5 years. TPPPS consists of 3 main pain categories:

- Vocal expression of pain (composed of 3 pain behaviors).
- The facial expression of pain (composed of 3 pain behaviors).
- Bodily expression of pain (composed of 1 pain behavior).

The minimum score in TPPPS would be 0 (no pain) and the maximum score 7 (most severe pain). It is best used for *postoperative pain* with satisfactory reliability and good validity (Tarbell et al. 1992; von Baeyer and Spagrud 2007; McGrath et al. 2008).

Parents' Postoperative Pain Measure (PPPM)

PPPM was introduced in 1996 by Chambers et al. and been used for 2–12 years old children. It includes 15 items each scored 0 or 1 (a dichotomous approach using **YES** or **NO** basis for parents); hence, the scores will range from a minimum of 0 to a maximum of 15. PPPM has good reliability and high validity. Its unique feature is that PPPM measures *postoperative pain at home* using parents' assessments with high reliability and good validity (Chambers et al. 1996; von Baeyer and Spagrud 2007; McGrath et al. 2008).

Assessment of Sedation

The scales used for assessment of sedation in the clinical setting of pediatric intensive care unit (ICU) are numerous; however, these scales are the main scales used for this purpose.

Ramsay Sedation Scale (Ramsay)

1. Sedation Agitation Scale (SAS).
2. Richmond Agitation Sedation Scale (RASS).

The scales are clinical assessment scales; it means that patient arousal state and responsiveness are the basis for their assessment.

Ramsay Sedation Scale (Ramsay)

Ramsay sedation scale was first introduced in 1974 and has been widely used thereafter. On this scale, 6 scores are arranged from 1 to 6 (Table 1). The "cooperative, orientated, and tranquil" patient is scored 2 (Ramsay et al. 1974).

Table 1 A summary of the Ramsay sedation scale

Score	Clinical description
1	Patient anxious and agitated or restless or both
2	The patient was cooperative, orientated, and tranquil
3	Patient asleep, ***responds*** to commands
4	Patient asleep, with a ***brisk*** response to a light glabellar tap or loud auditory stimulus
5	Patient asleep, with a ***sluggish*** response to a light glabellar tap or loud auditory stimulus
6	***Unresponsive*** to any stimulus

Richmond Agitation Sedation Scale (RASS)

RASS needs minimal training and less than 1 min is needed for the assessment of the patient using this scale. However, RASS should be determined in the very first assessment of patient arousal state to see if the patient is "alert and calm" equaling "zero." Then, throughout ICU care, the patient should be reassessed using the Confusion Assessment Method in the ICU (CAM-ICU) and be rechecked (Table 2). In brief, RASS has 10 grades ranging from +4 to −5:

- +4 to +1: combative to restless stages.
- 0 (zero score): "alert and calm" patient.
- −1 to −5: drowsy to unarousable patient.

The interested reader could find the full scale in Sessler et al. and Ely et al. (Sessler et al. 2002; Ely et al. 2003).

Sedation Agitation Scale (SAS)

SAS is shorter than RASS; it starts from 1 and leads to 7. SAS has 7 scores (without negative scores); while, a score of 4 stands exactly in the middle and is for the "calm and cooperative patient" (Table 3) (Riker et al. 1999; Simmons et al. 1999).

Table 2 A summary of the Richmond agitation sedation scale (RASS)

Score	Clinical term	Stimulus
+4	Combative	VOICE (verbal stimulation)
+3	Very agitated	
+2	Agitated	
+1	Restless	
0	Alert and calm	
−1	Drowsy	
−2	Light sedation	
−3	Moderate sedation	
−4	Deep sedation	TOUCH (physical stimulation)
−5	Unarousable	

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Table 3 A summary of the sedation agitation scale (SAS)

Score	Clinical term
7	Dangerous agitation
6	Very agitated
5	Agitated
4	Calm and cooperative
3	Sedated
2	Very sedated
1	Unarousable

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Near-Infrared Spectroscopy (NIRS)

Though introduced in laboratory studies for nearly 40 years, this is just about a decade that NIRS has been used in the clinical setting as CNS monitoring.

Nearly 40 years have passed since the time Professor "Frans Jöbsis" introduced the technology of "*near-infrared spectroscopy*" (NIRS) for clinical application as a monitor in 1977 (Wolf et al. 2007).

The monitor is at times known as cerebral oximetry because the frontal area of the cortex is the most common site for its application; however, other parts of the body, for example, the flanks, have been used frequently during the previous years as an index of somatic perfusion and oxygenation status; hence NIRS is often the generally accepted term.

NIRS is used in many clinical states and procedures including cardiac surgery; in cardiac surgery, NIRS is an important component of "***perioperative multimodal CNS monitoring.***"

Both animal models and human studies have demonstrated its usefulness; though some controversies may exist, including some types of cyanotic patients; these studies at times question the effect of NIRS application on patient outcomes [especially the systematic review recently published by Zheng et al. (Zheng et al. 2013)]. Also, other studies have some other considerations, especially for pediatric congenital heart surgery patients (Gottlieb and Mossad 2014).

NIRS has these advantages:

- Monitoring is noninvasive, providing real-time, continuous data,
- Monitors not only the CNS status but also, some aspects of hemodynamics since it monitors both oxygenation and perfusion status (i.e., mandates appropriate hemodynamics of CNS),
- During all the perioperative period, NIRS has its merits,
- During cardiopulmonary bypass or cardiac arrest, NIRS still works, not needing a pulsatile flow like pulse oximetry.

The technology of NIRS: near-infrared (NIR) light in the range of 700–1000 nm is radiated through self-adhesive optodes; then, penetration, passage, and reflection of NIR light through the skull or other underlying tissues; specific calculations are used for estimation of NIRS. However, the NIR light, when penetrated through for example skull bone, is partly absorbed by biologic chromophores like oxyhemoglobin (OHb), deoxyhemoglobin (HHb), and cytochrome oxidase; while the rest of the light is returned and is used for data measurement and calculations of the software to demonstrate the final refracted number of the oximetry; the calculations are based on the "modified Beer-Lambert Law."

Light reflection is the basic mechanism of NIRS; while light transmission through, for example, fingertip is used in pulse oximetry; this technological difference is the reason why we can attach the optodes of NIRS to the skull (for cerebral oximetry) or flank (for somatic and visceral oximetry); finally demonstrating the figures of rSO2 on the monitor screen. The NIRS optodes have several "light-emitting diodes" (LEDs) (Fig. 1).

NIRS compares each patient with himself/herself; it means that for each patient, a baseline is measured the first time; then, on a real-time basis, any subsequent change is compared with the baseline: more than 20% change is considered as a significant change needing some intervention to restore NIRS numbers to normal. Also, the absolute number for NIRS is defined from 40 to 90 (Fig. 2).

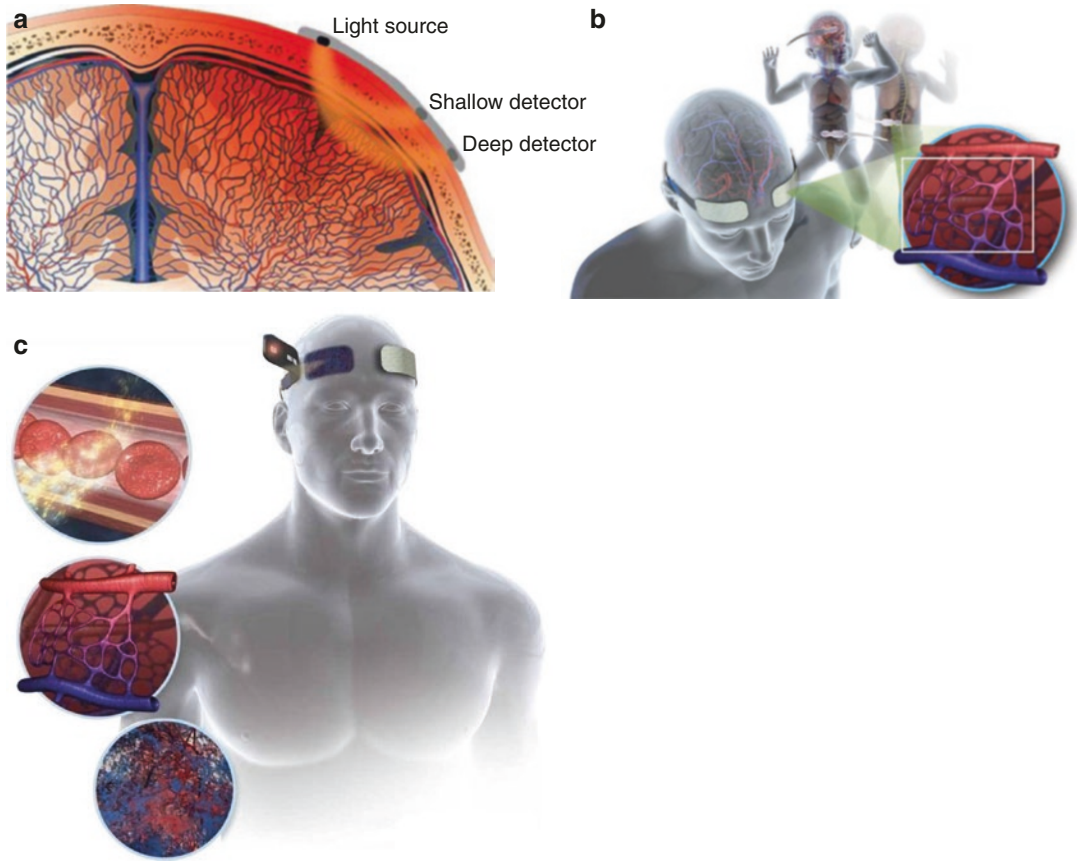

Fig. 1 (**a**) Schematic drawing of light transmission through the skull with two depths of light penetration with resultant regional values; (**b**) the final figures of NIRS are the result of a balance between tissue oxygen supply and consumption; (**c**) mechanism of NIRS in the microvasculature. (Published with kind permission of © Medtronic, 2016. All Rights Reserved)

Fig. 2 Intraoperative bilateral NIRS for cerebral oxygenation monitoring. (Published with kind permission of © Medtronic, 2016. All Rights Reserved)

What NIRS measures: NIRS measures the O_2 content of the target tissue; the final figures are the result of a balance between tissue oxygen supply and consumption (Fig. 1); in other words, the trend of NIRS shows the trend of changes in tissue oxygen content. But, what factors affect tissue oxygen content?

In brain tissue, the following factors are among the main ones affecting cerebral oxygen content:

- ***Cerebral tissue oxygen delivery*** to the organ through the blood which is determined by arterial oxygen saturation, hemoglobin, and arterial oxygen content,

- ***Cerebral hemodynamic***: several factors alter cerebral hemodynamics:
  - *Systolic, diastolic, and mean arterial pressure*; hypotension decreases tissue oxygen delivery; carotid stump pressure is the most important pressure.
  - *Patency of cerebral arteries* due to any underlying obstruction (permanent or transient), for example, due to extraordinary rotation of the head could affect tissue oxygen delivery; mechanical impedance against blood flow decreases tissue oxygen delivery.
  - *Vasoactive drugs* strongly affect cerebral blood and oxygen delivery.
  - *Cerebral venous drainage* (including any hindrance in cerebral veins) decreases tissue oxygen delivery.
- ***Cerebral tissue oxygen expenditure*** which is determined by cerebral tissue metabolism.
  - *Seizure* activity or *fever* increase tissue oxygen consumption.
  - *Level of anesthesia* (including sedation or consciousness state) affects the level of cerebral activity; the deeper the patient, the less oxygen demand; insufficient anesthesia level increases tissue oxygen consumption.
  - *Tissue temperature* affects tissue metabolism and hypothermia decreases tissue oxygen demand.

Practical notes for using cerebral NIRS: there are several notes that one should consider during clinical practice for using cerebral NIRS:

- Correct attachment of the probes: the underneath of the probes should be fine with no hair beneath; also, when using two probes, they should be symmetrical.
- For neonates and small children, either a neonatal probe should be used or one probe should be attached to the frontal area; however, when one probe is used, the differentiation property between right and left perfusion through carotids is not well gained; this is why using separate probes for each side of the frontal area is recommended.
- Baseline figures should be taken for each patient and they are very important; each patient is compared with its baseline.
- NIRS has been traditionally known as a CNS monitor; however, it has recently been used in pediatric patients and neonates as a "***somatic monitor***"; so, it could monitor other tissues to check if their oxygenation is appropriate; some parts of the body like splanchnic perfusion, renal perfusion, and spinal cord perfusion (Fig. 3). The difference between somatic and cerebral NIRS should not be more than 15–20; increased difference suggests a drop in cerebral tissue oxygen content and its etiology should be sought. Usually, somatic NIRS readings are higher than cerebral NIRS; but, if somatic NIRS drops, there is something wrong with somatic perfusion; mandating a revision of the whole body perfusion state. This is why both cerebral and somatic NIRS could be used as appropriate surrogates for the treatment of perfusion impairments, for both regional and global impairments (Nelson et al. 2008; Murkin and Arango 2009; Tweddell et al. 2010; Gil-Anton et al. 2015).
- When considering the ***postoperative period***, acceptable NIRS results (cerebral and especially somatic) could be good predictors for successful weaning and extubation (Gil-Anton et al. 2015).
- In patients with extracorporeal support devices (including ECMO, RV, or LV assist devices) NIRS could be of very good benefit (Papademetriou et al. 2012).
- Some species of ***hemoglobin*** (like a sickle cell) or very high concentrations of hemoglobin (e.g., patients with severe polycythemia) might have interference with real results of cerebral NIRS; other factors like skin pigmentation, ambient light, or injected dyes might produce interference (Gottlieb and Mossad 2014).
- Underlying cardiopulmonary impairments, anemia, or vascular diseases might be confounders of NIRS readings.

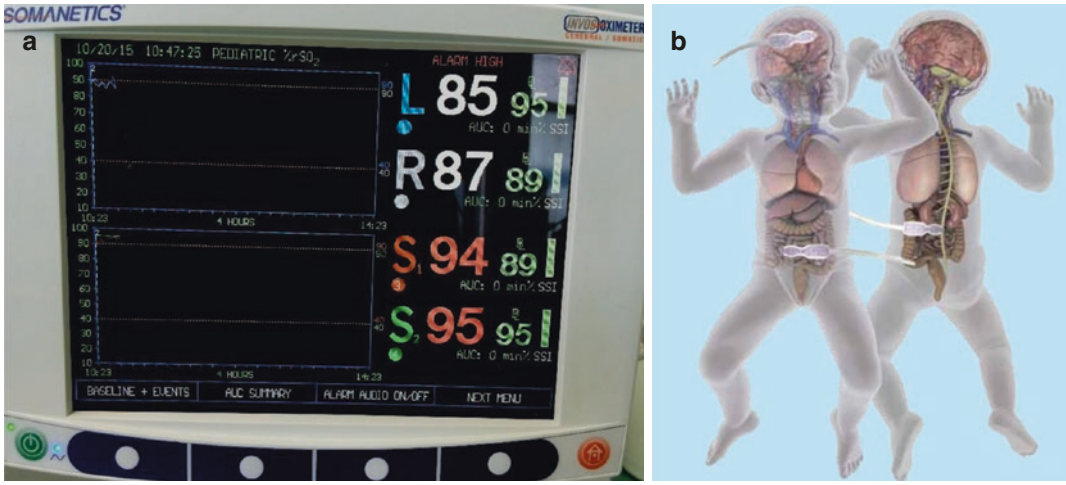

Fig. 3 (**a**) Intraoperative NIRS demonstrating both cerebral and somatic NIRS; the lower half of the monitor panel shows the results of somatic optodes (S_1 and S_2); (**b**) schematic drawing of cerebral and somatic NIRS. (Published with kind permission of © Medtronic, 2016. All Rights Reserved)

In clinical practice, any decline in regional cerebral NIRS reading often needs an algorithmic approach involving the following steps (Denault et al. 2007; Murkin and Arango 2009):

1. Turn the position of the head to a neutral position to relieve any underlying mechanical obstruction due to excessive lateral rotation.
2. Ask the surgeon to control the position of arterial and/or venous cannula to relieve obstructions in blood flow.
3. Correct hypotension (especially mean arterial pressure).
4. Diagnose and treat any underlying systemic desaturation (blood gas and/or pulse oximetry).
5. Correct excessive hyperventilation; $PaCO_2$ especially below 35 mmHg should be corrected.
6. Diagnose and treat anemia especially when hematocrit is below 30%.
7. Check cerebral oxygen consumption state; treat any underlying seizure or convulsive activity; detect any episodes of hyperthermia or fever and treat them; check the level of anesthesia or sedation and add the depth of anesthesia or sedate the patient more as needed.
8. Diagnose and treat any underlying pump failure; including possible failing heart or inadequate flow of pump or inadequate perfusion by assist devices and treat them; modalities like echocardiography, jugular venous blood oxygen saturation ($SjVO_2$) or metabolic assessments like lactate level could be useful guides.
9. Diagnose and treat any possible etiologies causing cerebral edema and/or increased intracranial pressure; diagnose with imaging modalities or intracranial pressure monitors and treat increased ICP with positioning and medical treatments.

Electroencephalography (EEG) Including Traditional EEG, qEEG, and CCEEG

History of EEG

EEG is an invention by the German psychiatrist Hams Berger who described the electrical recordings of the brain in 1926 for the first time; his records are still valid. Nowadays, after decades and also, with improvements in this technology, EEG is still a very useful diagnostic and monitoring tool; though it is considered a "***good***" CNS monitoring but not a "***perfect***" one.

Here we discuss EEG in two main topics:

1. The basic standards of EEG include basic technical requirements and how EEG works.
2. Using EEG in the perioperative period as a continuous CNS monitor.

In both of the above segments, we will always consider two age ranges:

1. Adult and older pediatric patients.
2. Neonates and small pediatric group.

The current discussion on EEG has contributions from 2 main sources:

- The guidelines published by the American Clinical Neurophysiology Society (1994; 2006a, 2006b; Herman et al. 2015a, 2015b); a list of the guidelines and statements of the American Clinical Neurophysiology Society is available at its website: https://www.acns.org/practice/guidelines
- The guidelines and statements released by the American Society of Neurophysiological Monitoring (Isley et al. 2009); their position statements are available at: http://www.asnm.org/

What Are the Applications of EEG in the Perioperative Period?

There are some main reasons for using EEG in the ***perioperative period***, including (Isley et al. 2009; Edmonds Jr. et al. 2011):

1. Detection and diagnosis of any ***underlying CNS pathology*** or any ***baseline disorder***; for this purpose, it is important to have a baseline EEG for further assessments and documentation; this is especially a major consideration in patients with underlying disease or potential risk factors for ischemia.
2. Detection and documentation of any ***new abnormality*** in CNS function in the perioperative period; these new findings should be diagnosed and if needed, be treated so soon.
3. As a ***continuous monitoring device*** and a real-time neurologic assessment tool, a ***diagnostic tool***, for detection of seizure or other CNS events, like coma, brain death, drug toxicities, or the possibility of residual anesthetic effects.
4. Titrating the dosage of ***anesthetics*** and ***sedatives*** during the perioperative period.
5. During early ***rewarming from cardiopulmonary bypass***, often an imbalance between brain oxygen demands and oxygen delivery occurs which could be a potential etiology for brain ischemia.
6. A ***therapy tailoring guide*** which is used for monitoring the dosage of anticonvulsants and their efficacy in controlling clinical and subclinical seizure activity; so, EEG works as a guide for titration of drug dosage (like anticonvulsant dose) to guarantee drug efficacy.
7. In a barbiturate-induced or hypothermia-induced coma, when we need objective confirmation of "***cortical silence***"; which needs monitoring the efficacy of cerebral protection strategies during the perioperative period.
8. Tailoring appropriate critical perioperative care in patients at risk of even borderline ischemic events; for example, prevention of adverse effects of ***hyperventilation*** on cerebral perfusion, prevention of deleterious effects of acute ***hemodilution*** (both intraoperative, during cardiopulmonary bypass, or postoperative), and prevention of adverse effects during ***rewarming*** from cardiopulmonary bypass or hyperthermia in the postoperative period.

How EEG Works (Including the 10/20 System and the Waves)

The standard electrode system is the 10/20 electrode system of the International Federation of Clinical Neurophysiology and the American Clinical Neurophysiology Society (Klem et al. 1999; 2006e; Isley et al. 2009).

The main source for EEG waves is the postsynaptic activity of cortical neurons; these neurons, called "pyramid" cortical cells or "Betz" cells, are located in the outermost layer of the brain cortex just underneath and perpendicular to the skull.

Having very long axons extending toward the inner parts of the brain; EEG is the summative activity of millions of these pyramids; that is, only the ***post-synaptic*** electrical currents of pyramids (both excitatory and inhibitory functions) accumulate and create EEG waves; however, the axonal activity does not contribute in the production of EEG waves. Often, the following characteristics are considered the main features of EEG waves:

1. *Frequency*: the number of times that each wave occurs in each second, presented as Hz; each EEG wave is usually consisted of at least 2 basic waves which are overlapped together and compose the final waves; the composing waves could be analyzed by Fourier analysis; Table 4 is a summary of basic EEG waves; we could use this mnemonic for EEG waves GBATDS.
2. *Time*: is demonstrated on the horizontal axis of EEG records.
3. *Amplitude*: EEG waves have an amplitude between 10 and 100, 100 μV; which is about 100 times less than the amplitude of electrocardiography waves; with increasing age, the amplitude of EEG waves decreases.
4. *Symmetry*: one should always seek symmetry in EEG waves between the 2 hemispheres even in the anesthetized patient.
5. *Voltage*: the EEG electrodes record the difference in their voltage between two electrodes across the time scale, in other words, deflections above or below the horizontal scale are the result of the voltage difference between the two electrodes: negative "voltage difference" between the first and the second electrodes would be demonstrated as ***above the scale deflection*** (i.e., up deflection); while the posi-

Table 4 Normal EEG rhythms; that is, EEG waves (mnemonics: GBATDS)

Wave category	Symbol	Frequency	Amplitude and/or voltage	Related activity	Clinical equivalent
Gamma rhythm	γ	25.1—55 Hz	High voltage and amplitude	Cortico-thalamic perception; both during wakefulness and sleep	Engaged in: • Sensory processing activities, • Perception process.
Beta rhythm	β	12.6–25 Hz	In adults 10–20 μV	Cortico-cortical network	Fully awake patient with: • Open eyes • Mental activity
Alpha rhythm	A	8–12.5 Hz	Relatively high voltage and amplitude: 30–50 μV In adults: 10–20 μV	Mainly composed of electrical activity emerged from parietal and occipital lobes of the cortico-thalamic network	• Awake, but the relaxed individual with closed eyes • Equals drowsy state
Theta rhythm	*θ*	4–8 Hz	50–100 μV In adults: 10–20 μV	• Often seen in temporal lobes in the awake state but sleepy and relaxed • and cortico-thalamic activity and limbic activity	• Equals stage 2 of sleep (i.e., light sleep) or drowsy state • Also, frequently seen in young children
Delta rhythm	*δ*	1–4 Hz	High amplitude 100–200 μV	Cortico-thalamic dissociation	• Equals deep dreamless sleep (stage 3 of non-REM sleep); so helps define the depth of sleep • Another name is slow-wave sleep • Also, seen during coma or other brain disorders • Finally, seen in infancy
Slow rhythm		<1 Hz			

tive difference between the first and the second electrodes would appear as ***below the scale deflection*** (i.e., down deflection) on EEG.

EEG function is composed of thousands of EEG ***epochs***; each epoch is an interval of "few seconds"; which records electrical activity in this time domain and is usually 2–4 s; then, the electrical activity of each epoch is analyzed by the device microprocessor and demonstrated as EEG waves on a time-based scale.

Electrode arrangement on the scalp: the standard order of EEG electrode arrangement on the scalp is named "***montage of electrodes***." Four main anatomic landmarks are used for electrode attachment over the scalp:

- Anterior location: nasion.
- Posterior location: occipital or inion.
- Two pre-auricular locations.

The above locations combined with alphanumeric coding are used to name the standard electrode positions; which helps us locate the lesions and also, to compare similar anatomical points on the two hemispheres (Fig. 4):

- F: Frontal electrodes.
- O: Occipital electrodes.
- P: Parietal electrodes.
- T: Temporal electrodes.
- C: Central electrodes.
- A: Auricular electrodes.
- M: Mastoid electrodes.
- even numbers as subscripts demonstrate the right hemisphere,
- odd numbers as subscripts demonstrate the left hemisphere,
- *z* as subscript demonstrate midline electrodes (*z*: zero),

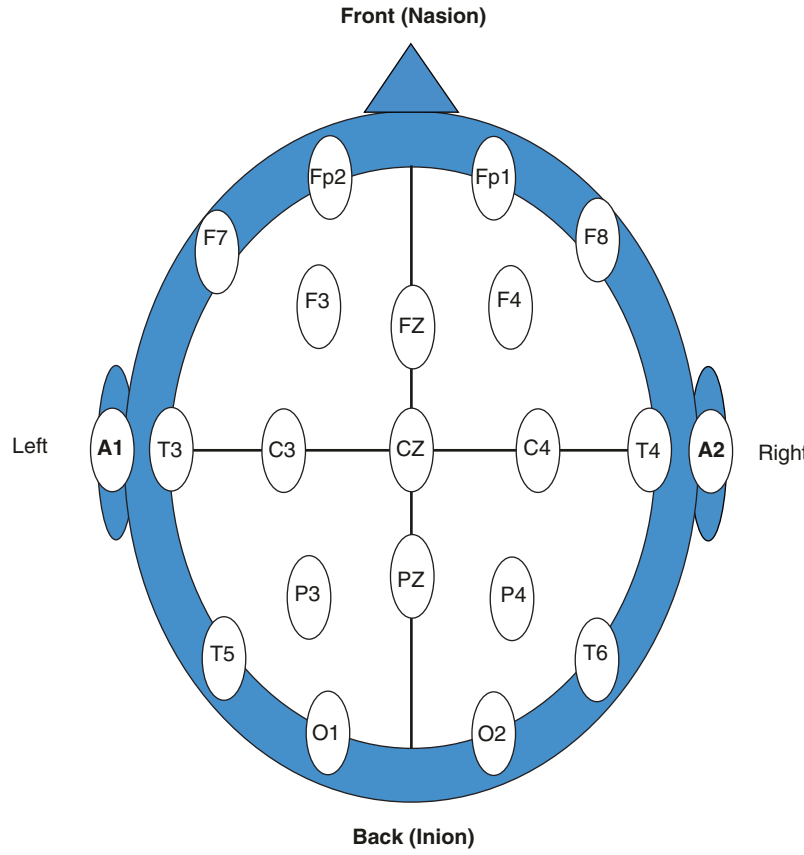

Fig. 4 EEG electrode arrangement on the scalp

Guideline 5 of the American Clinical Neurophysiology Society describes the standard electrode position nomenclature (2006e).

The standard electrode system: the standard 10/20 electrode system could be used to have the standard 16 channel systems in recording conventional EEG; for intraoperative or postoperative CNS recording, we usually use 2–8 channels; and even many times during the perioperative period, only 3 electrodes are used which are attached on the frontal area: two of them are used to record the neuronal electrical activity as "differential amplifier with voltage difference" while the third electrode is the "mandatory reference signal" electrode. Although, some authors believe that at least 8 channels should be used. How we use the electrodes for electrode montage is described fully in Guideline 6 of the American Clinical Neurophysiology Society: A proposal for standard montages to be used in clinical EEG (2006f).

Grounding electrode: according to the American Clinical Neurophysiology Society guideline (2008 version) except for several situations, we should always use a grounding electrode; these exceptions include those patients in which other electrical types of equipment are attached to the patient (like operating room or intensive care units); in these latter patients, we should avoid double grounding.

Different types of electrodes are available. However, it is more important to follow instructions for use more than just the electrode type; that is, a constant type of electrode should be used for electrode ***montage***; for artifact prevention, the electrodes should be well attached, appropriate electrode quality should be guaranteed and finally, enough gel should be pasted to prevent any extra resistance and guarantee the low amount of impedance. The three-electrode types are cup electrodes, silver–silver chloride electrodes, and needle electrodes:

- "Cup" electrodes which are usually made from "tin, silver, or gold,"
- "Silver–silver chloride" electrodes are the third type of EEG electrodes,
- Gold disks or silver–silver chloride disks adhered to collodion are the best options; while other good quality electrodes are acceptable,
- Needle electrodes are not recommended unless in very special condition with related precautions,
- All these 3 types of electrodes should be free of inherent noise; keep electrodes clean to decrease noise,
- Besides the good quality of electrodes, guaranteed adhesion with enough gel, and keeping electrodes clean, the EEG cables and wires should be avoided from the vicinity of other cables to prevent noise and improve signal quality; shielding the EEG leads also could improve the quality,
- Special care should be given to prevent the transmission of contagious diseases like HIV, Creutzfeldt–Jakob disease, viral hepatitis, or other similar agents.

Interpretation of EEG

For EEG interpretation, some variables should be considered; though this is far beyond the scope of this book; however, a summary of those indices which suggest abnormality is mentioned here:

- ***Asymmetry***: there should be symmetry between right and left hemispheres; asymmetry is suggestive of pathology; asymmetry could be a sign of ischemia or arterial occlusion.
- ***Spikes***: the spike waves are suggestive of seizure activity which may or may not be accompanied by clinical convulsion.
- ***Decreased frequency, decreased voltage, and decreased amplitude***: during early stages of ischemia, the frequency of waves decreases while the voltage is preserved; in early ischemia, decreased frequency of waves is seen while the voltage of EEG waves is preserved; however, with more severe ischemic time, both wave frequency and voltage are depressed; if there is an EEG ***amplitude*** drop more than 30% or there is more than ***30 s*** time interval of EEG changes, it should be consid-

ered with great caution as important indicators of ischemia.
- ***Normal EEG waves seen in abnormal states***: this could also be a sign of pathology (e.g., if the appearance of delta waves in an unusual state could be an indicator of a brain lesion).

The abnormal EEG changes are often specifically seen as a significant decrease in "beta and the alpha" waves. Also, the following abnormal characteristics are seen in these patients:

- Newly occurred abnormalities are often seen in the left hemisphere in the postoperative period,
- More invasive, more complex or longer procedures create many severe postoperative changes,
- Postoperative CNS ischemia (CBF < 22 mL/100 g/min) changes EEG waves from normal to ischemic patterns whenever cerebral blood flow.
- One should always consider the effects of altered hemodynamic status, temperature, and anesthetic drugs on EEG findings, especially when interpreting abnormal waves,
- Injuries due to cardiac surgery are similar in EEG to "organic brain syndrome" findings.

How to Report EEG

Based on Guideline 7 of the American Clinical Neurophysiology Society, each report is recommended to be prepared under 4 main sub-classes; a full description could be found in the guideline text (2006g); however, briefly speaking, the following items are the main components of an EEG record:

1. ***Basic patient information***: including age, sex, name, EEG identification number.
2. ***Introduction of the report***: how the patient was prepared; including any received drugs for sedation, sleep deprivation, fasting state, how many electrodes from the standard 21 electrodes of the 10/20 system were used and how long was the total recording time.
3. ***Description of the report***: should include all findings, both normal and abnormal, away from interpretation; this interpretation should include all the findings in such a way that whenever another clinician reads the record, could reach a decision even without looking at the EEG recordings.
4. ***Interpretation of the report*****:** interpretation should be prepared having these two parts: ***impression & clinical correlation***.
   (a) ***Impression*** is the subjective finding of the interpreter about the *normality or abnormality of EEG*; it should not be too long and if it has any abnormality, should contain the main 2–3 findings.
   (b) ***Clinical correlation*** is the other part that should be mentioned in the "*interpretation of EEG*" and it should correlate the EEG findings with the clinical picture. If the EEG findings are mild, the phrase "*minor irregularities in cerebral function*" is suggested in the report; however, if it is more than mild, the term "*cerebral dysfunction*" is appropriate for the interpretation of the report. These terms are appropriate for use in the record: "*findings of EEG are consistent with the diagnosis, or supportive of the diagnosis, or compatible with clinical findings*." If EEG findings are not compatible with clinical findings, it should be stated cautiously, in order not to directly question the clinical diagnosis. Also, if any medication has been used before EEG, it should be mentioned in the interpretation. Some samples of EEG could be added to the record, especially when using an electronic recording.

Limitations of EEG

There are several limitations to EEG and this is why we believe EEG is a "***good***" CNS monitoring but not a "***perfect***" one (Constant and Sabourdin 2012):

- EEG works through electrodes that are usually attached to the scalp. These electrodes report the electrical activity of the cortex; that is, the neurons located just beneath the cortical layer; however, this electrical activity does not

include the full activity of the sub-cortical parts of the brain including the nuclei; hence could not alarm ischemia in subcortical regions.
- Using conventional EEG in the perioperative period, especially inside the OR is a difficult task due to its technical complexities, it is sometimes really cumbersome and inconvenient; though newer modalities of EEG are much more used especially in the postoperative period.
- EEG is a biorhythm; so, it will be affected like other biorhythms like age, environment, and circadian variations.
- Ischemia in the perioperative period does not always present itself in the same manner; in other words, if the inhibitory neurons of the CNS suffer an ischemic insult, the result in EEG would be EEG overactivity.
- EEG could detect abnormalities including ischemia; however, it could not detect the location of ischemia (ischemic site), definite mechanism of ischemia (the exact etiology), or the anatomic zone of ischemia (the scope of injury).

EEG Considerations in the Pediatric and Neonatal Group

The basic principles are the same; especially, EEG in older children and adolescents has many similarities to adult EEG; however, neonates, infants, and younger pediatric patients need special consideration regarding the age-specific interpretations (De Weerd et al. 1999; Husain 2005).

Amplitude Integrated EEG: aEEG

This version of EEG is used much more recently in critical care of CNS; aEEG is a bedside tool for neurophysiologic assessment; uses fewer channels than standard EEG; so, aEEG is much easier, both regarding its use and interpretation, and could help earlier diagnosis much more than conventional EEG; however, standard EEG is more sensitive for the diagnosis of seizure. However, aEEG does not need to be interpreted exclusively by a neurologist. Of course, standard EEG remains the decisive method of diagnosis for neurophysiologic assessments. In neonatal ICU, unless we use aEEG in NICU, a considerable part of patients with neonatal seizures would be undetected (Boylan et al. 2015; Kang and Kadam 2015).

EEG spectrogram: this method has been introduced as a new processing method to describe the effects of different anesthetics as EEG waves; however, a 3-dimensional model is used which describes the Power, Amplitude, and Frequency of EEG waves; power is calculated as 10 log10 (amplitude). Changes the resulting 3-dimensional graph as a 2 D colored graph; the 3-dimensional graph is named the "Compressed Spectral Array" (CSA). In these records, each of the spectra is calculated based on 3 s interval while every 2 adjacent spectra have overlaps of 0.5 s (Purdon et al. 2013; Ching and Brown 2014; Purdon et al. 2015).

For more detailed information, the interested author could refer to "Minimum technical standards for EEG recording in suspected cerebral death" which is discussed in detail in Guideline 3 (2006c). Also, "Standards of Practice in Clinical Electroencephalography" are discussed in detail in Guideline 4 (2006d). Besides, Guideline 7 is the guideline that discusses fully the method of writing EEG reports (2006g).

Transcranial Doppler: TCD

TCD was first described in 1982 by Rune Aaslid. It is a non-invasive neuromonitoring device that measures the velocity of blood flow through cerebral arteries. When invented, TCD was designed to be a simple device with simple technology, which could be frequently used for neuromonitoring; however, not many people can be considered enough skilled in using the device. TCD has the following characteristics:

- non-invasive neuromonitoring,
- high temporal resolution,
- continuous, frequent, repeatable, and reproducible measurements of CBF velocity,
- rapid and accurate assessments with a high probability,

- real-time monitoring (which could be used easily at the bedside or in the operating theatre),
- never reported having any complication,
- relatively low price,
- may be used as monitoring for up to several hours (including the postoperative period),

How TCD works: low frequency (1–2 INCLUDEPICTURE "http://www.ncbi.nlm.nih.gov/corehtml/pmc/pmcents/x2009.gif" * MERGEFORMATINET MHz) ultrasonic Doppler signal is used in TCD, through pulse-waved Doppler; the Doppler beam calculates the blood flow velocity based on "Doppler shift." Doppler waves are projected from the piezoelectric crystal in the TCD probe toward the tissue; then, these waves are reflected in the crystal; finally, the movement of RBCs inside the arterial lumen causes the Doppler to shift. The angle of insonation is a very important factor.

TCD calculates blood flow velocity in different CNS arterial systems, including Anterior, Middle, and Posterior Cerebral Arteries (i.e., ACA, MCA, and PCA) and also, Internal Carotid Arteries (ICA) (Alexandrov et al. 2012).

Blood flow velocity especially in the middle cerebral artery (V_{MCA}) is the main index measured by TCD when used for monitoring in the perioperative period of cardiac surgery

The following variables are measured by TCD for each of the insonated arteries (Nelson et al. 2008; Wang et al. 2010):

(i) ***Peak Systolic Velocity*** (PSV).
(ii) ***End Diastolic Velocity*** (EDV): which is often 25–50% of PSV.
(iii) ***Mean Velocity*** (MV) is calculated using this formula:

$$\mathrm{MV} = \left[\mathrm{PSV} + \left(2 \times \mathrm{EDV}\right)\right] / 2$$

(iv) ***Pulsatility Index (PI)*** also known as Gosling's Pulsatility Index is the resistance in each cycle of blood flow through cerebral arteries; for calculation of PI, this formula is used:

$$\mathrm{PI} = \left(\mathrm{PSV} - \mathrm{EDV}\right) / \mathrm{MV}$$

PI values could be assessed with TCD (Fig. 9). The normal value for PI is from 0.5 to 1.19. If PI is below 0.5, it demonstrates proximal arterial occlusion or stenosis; the occlusion or stenosis in proximal arteries causes arteriolar vasodilation and decreases the above ratio which calculates PI. On the other hand, if any occlusion, stenosis, or vasoconstriction occurs in distal arterial segments, PI increases above 1.19. Another clinical state decreasing PI to less than 0.5 is "arteriovenous malformation: AVM"; in AVM, the distal connection to the venous system decreases distal resistance, and PI goes well below 0.5. On the other hand, increased intracranial pressure "increased ICP" increases PI; so, ICP and PI have the same directions for change; each 1 mmHg increase in ICP causes a 2.4% increase in PI (Nicoletto and Burkman 2009a, 2009b).

(v) ***Resistance Index (RI)*** also known as Pourcelot Resistance Index is used for the calculation of arterial resistance to blood flow and is calculated by this formula:

$$\mathrm{RI} = \left(\mathrm{PSV} - \mathrm{EDV}\right) / \mathrm{PSV}$$

Normally, a RI > 0.8 is an index of increased resistance, and the diagnosis list for increased RI is similar to PI (White and Venkatesh 2006; Naqvi et al. 2013).

When we think about the final CNS outcome, one should always consider the relationship between oxygen supply–demand with special attention to critical situations like the period of cardiopulmonary bypass "CPB." Though the innate cerebral autoregulation mechanisms protect the brain during blood pressure "ups" and "lows," these "***safety mechanisms***" could be impaired in special situations: ***they may be impaired to varying degrees during and somewhat, after CPB***. Among all neuromonitoring

modalities, TCD measures Cerebral Blood Flow (CBF) during and after CPB. CBF is a function of Cerebral Perfusion Pressure (CPP) and Cerebral Vascular Resistance (CVR). Meanwhile, CPP is the algebraic result of Mean Arterial Pressure (MAP) minus Intracranial Pressure (ICP); that is, CPP = MAP−ICP. So we will have:

$$\mathrm{CBF} = \left(\mathrm{MAP} - \mathrm{ICP}\right) / \mathrm{CVR}$$

Among all cerebral arteries, often the best waveform pattern is gained through Middle Cerebral Artery (MCA), because of better bony window through the temporal bone, especially in adults and children with closed fontanels. Measurement of the "angle-corrected flow velocity" is usually not as exact for ACA and PCA as the MCA measurements; this is an important reason why in the majority of patients, we use MCA for perioperative TCD monitoring (Hayashida et al. 2004).

Based on clinical and experimental studies on the cerebral arterial system, the following factors are considered as the confounders of the blood velocity calculated by TCD; they might affect blood velocity calculated by TCD and should be considered during TCD (Brass et al. 1988; Vriens et al. 1989; 1993; Trindle et al. 1993; Poulin et al. 1996; Torbey et al. 2001; Kassab et al. 2007; Rasulo et al. 2008; Purkayastha and Sorond 2012; Naqvi et al. 2013):

- ***age***: in human brain circulation, the lowest CBF is after birth, which is about 25 cm/s; however, CBF increases to its peak at 4–6 years after birth, peaking up to 100 cm/s; between 20 and 70 years, CBF decreases with a steady-state slope, decreasing 0.3–0.5% per year and finally reaches to 40 cm/sec at the seventh decade of life.
- ***Hematocrit***: has an inverse relationship with CBF, drops in hematocrit increase CBF by up to 20%.
- ***Gender***: CBF is a bit higher (10–15%) in premenopausal women; possibly to compensate for lower hematocrit levels.
- ***PaCO2*** (arterial pressure of CO_2): when $PaCO_2$ decreases, some degrees of cerebral vasoconstriction happens and causes increased CVR leading to decreased CBF; also, CBF increases in response to hypercapnia.
- ***MAP***: the underlying hemodynamic (especially MAP) status affects CBF; the relationship between MAP and CBF is linear.
- ***ICP (Intracranial Pressure)***: affects CBF directly.
- ***Blood viscosity***: when blood viscosity increases, the velocity of CBF decreases and vice versa.
- ***Depth of anesthesia*** and level of consciousness, including administration of analgesic agents or anesthetic drugs, could affect CBF and TCD results.
- ***Diurnal time pattern*** affects TCD through diurnal changes in blood pressure and CNS perfusion: the lowest CBF is seen at about 11 A.M.
- ***Patient posture*** affects the CBF: it is different in the seating position compared to the supine position.

Before fontanel closure, other arteries except for MCA could be used since their windows are pretty well. Add to this point that in neonates and small children, the difficulties in using TCD are less also due to the smaller skull bone layer and the smaller distance from the probe contact surface to the point of velocity calculation.

Indications for using TCD: there is a wide range of indications for using TCD; a detailed list of TCD standards and guidelines are available describing the physical and clinical standards and the requirements for using the device; however, for ***perioperative neuromonitoring*** of pediatric cardiac surgery patients, TCD is mainly used for the following reasons (Iida et al. 1997; Hoffman 2006; Alexandrov et al. 2007; Edmonds Jr. et al. 2011; Alexandrov et al. 2012; Ghazy et al. 2016):

- ***perioperative monitoring***: increasing attention has been drawn to TCD as one of the choice neuromonitoring modalities in patients undergoing DHCA and antegrade cerebral perfusion; especially in pediatric cardiac surgery especially for checking the CNS autoregulatory response due to effects of stimuli like hypercapnia or blood pressure fluctuations,

- ***Assessment of cerebral blood flow for prevention of hypo- or hyperperfusion***: detection of adequate cerebral blood flow during selective cerebral perfusion and antegrade cerebral perfusion especially associated with DHCA and low flow perfusion bypass for special procedures like aortic reconstruction. Also, measurement of cerebral flow rates during other modes of CPB. Besides, for adequacy of blood flow to CNS, TCD could be used for checking the correct position of the ***arterial or venous cannula*** during CPB. Another application is the assessment of hyperemia: a low CBF velocity ratio of MCA/ICA with a high mean flow velocity of the MCA could be predictive of critical hyperemia, especially in patients with critical state,
- evaluation of cerebrovascular ***autoregulation,***
- ***detection of embolism***: detection of microemboli load during CPB which is usually directed from the aorta to the brain circulation through MCA; during the post-DHCA period, there is an increased likelihood for the embolic load to CNS and TCD could help for its detection,
- detection of possible ***thrombosis,***
- ***detection of arterial stenosis***: stenotic regions inside the intracranial arterial system could be detected by TCD,
- monitoring intracranial pressure (**ICP**) by a non-invasive method,
- measurement of effective downstream pressure,
- diagnosis of ***brain death,***
- ***assessment of vasospasm***: evaluation of patency in CNS arterial system and to detect any underlying CNS arterial vasospasm,
- assessing the ***efficacy of anti-thrombotic therapies*** in reducing the platelet embolic load sent to CNS.

Windows for TCD Signal Acquisition:

TCD windows are divided into 2 main time intervals: before the closure of fontanels and after the closure of fontanels.

Before fontanels are closed, the following windows are recommended; of course, the probe used in such states is a fine bar-shaped probe, pretty much smaller than the conventional probes of TCD (Correa et al. 2004; Enriquez et al. 2006; Brennan and Taylor 2010; Steggerda et al. 2012):

1. **MCA** is assessed very well through the temporal bone.
2. **ACA and the circle of Willis** could be examined through anterior fontanel.
3. **Posterior cerebral circulation** could be evaluated through the foramen magnum or mastoid fontanel (i.e., posterolateral fontanel) which is located anatomically posterior to the mastoid process; mastoid fontanel is a good window, especially in preterm and term neonates.

After the closure of fontanels, the following windows are used mainly for TCD; though before the closure of fontanels, the windows are much more "open" for TCD. However, these are the standard windows:

Trans-temporal window is mainly located at the supra-zygomatic portion of the temporal bone and is used mainly for insonation of MCA while ACA and PCA could be assessed through this window by using special maneuvers (Figs. 5 and 6 and also Fig. 9); this window is used for TCD more than any other window (Table 5).

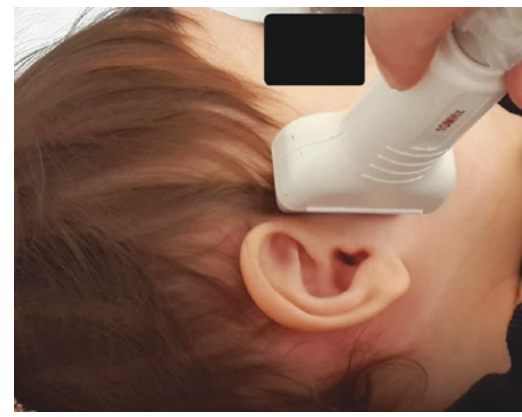

Fig. 5 Trans-temporal window (Courtesy of Dr. Tanghatari Neurology lab)

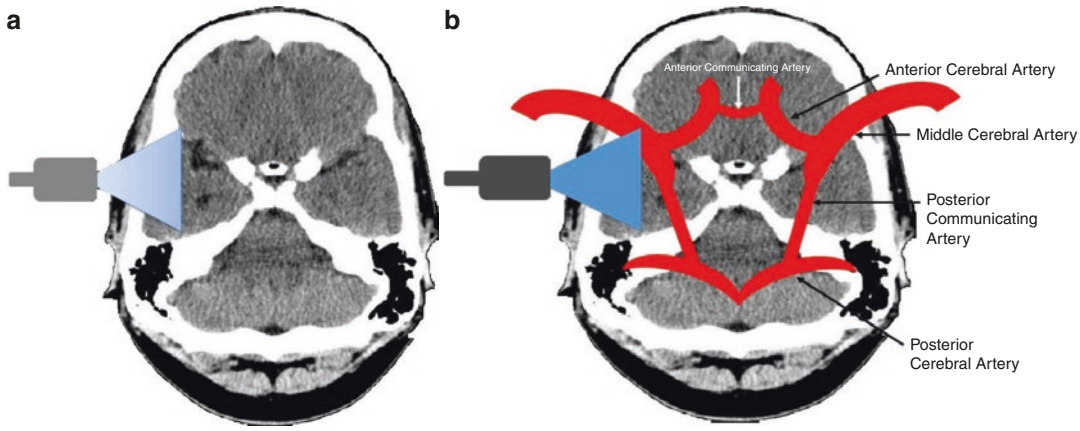

Fig. 6 (**a**) Schematic representation of trans-temporal window for Middle Cerebral Artery (MCA) with TCD; (**b**) a general presentation of other main cerebral arteries is demonstrated

Table 5 Desired depth of TCD insonation based on the head circumference in children

Diameter of head	Proximal MCA	Distal MCA
12 cm	30–54 mm	30–36 mm
13 cm	30–58 mm	30–36 mm
14 cm	34–62 mm	34–40 mm

This window needs a supine position. The examiner should draw an arbitrary line from the tragus of the ear to the lateral canthus of the eye; there is an area extending from this line up to about 2 cm; the probe head should be inserted here gently, perpendicular to the bony plate of the temporal bone with enough probe gel; MCA blood flow has a good correlation with total cerebral blood flow, this is among the reasons why using this window has gained great popularity. The sample volume of the TCD probe should be adjusted based on the diameter of the head. In the pediatric patient population, the desired depth is estimated based on the head circumference, described by Alexandrov et al. Table 2 (Alexandrov et al. 2007).

A Trans-orbital window is used for insonation through the orbit; usually for assessment of the ophthalmic arteries and in some patients, to examine some cavernous parts of ICA (known as the carotid siphon). It is recommended to decrease 10–15% of the probe power when using this window. The probe should be placed on the eyelid with the insonation angle a bit medial and upward (Fig. 7 and Fig. 9).

The retro-mandibular window is used to examine cervical parts of the carotid artery (Fig. 8 and Fig. 9).

The sub-occipital window is used to assess the posterior arterial system; it mainly consists of the basilar and vertebral arteries and is used for ACA and PCA. The transducer should be placed below and medial to the mastoid process while it is recommended to turn the patient to his/her side (Fig. 9).

What Are the Main Limitations of TCD?

Some difficulties impede the application of TCD, especially for longer intervals:

- difficulties in making reproducible measurements,
- like some other devices, depends highly on the operator,
- the correct angle of insonation; if insonation is not done with a correct angle, the calculations would not be exact,
- difficulties in finding an appropriate window which is seen more often in adults and older children,
- lack of regional blood flow assessments; instead, TCD calculates CBF velocity in main CNS arteries.

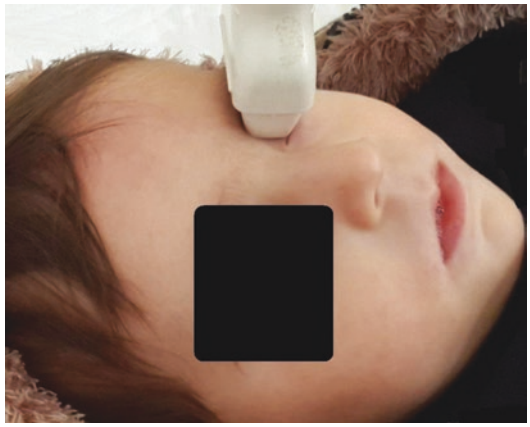

Fig. 7 Transorbital window (Courtesy of Dr. Tanghatari Neurology lab)

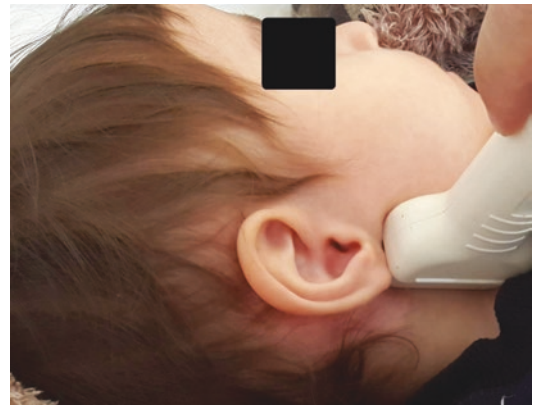

Fig. 8 Retromandibular window (Courtesy of Dr. Tanghatari Neurology lab)

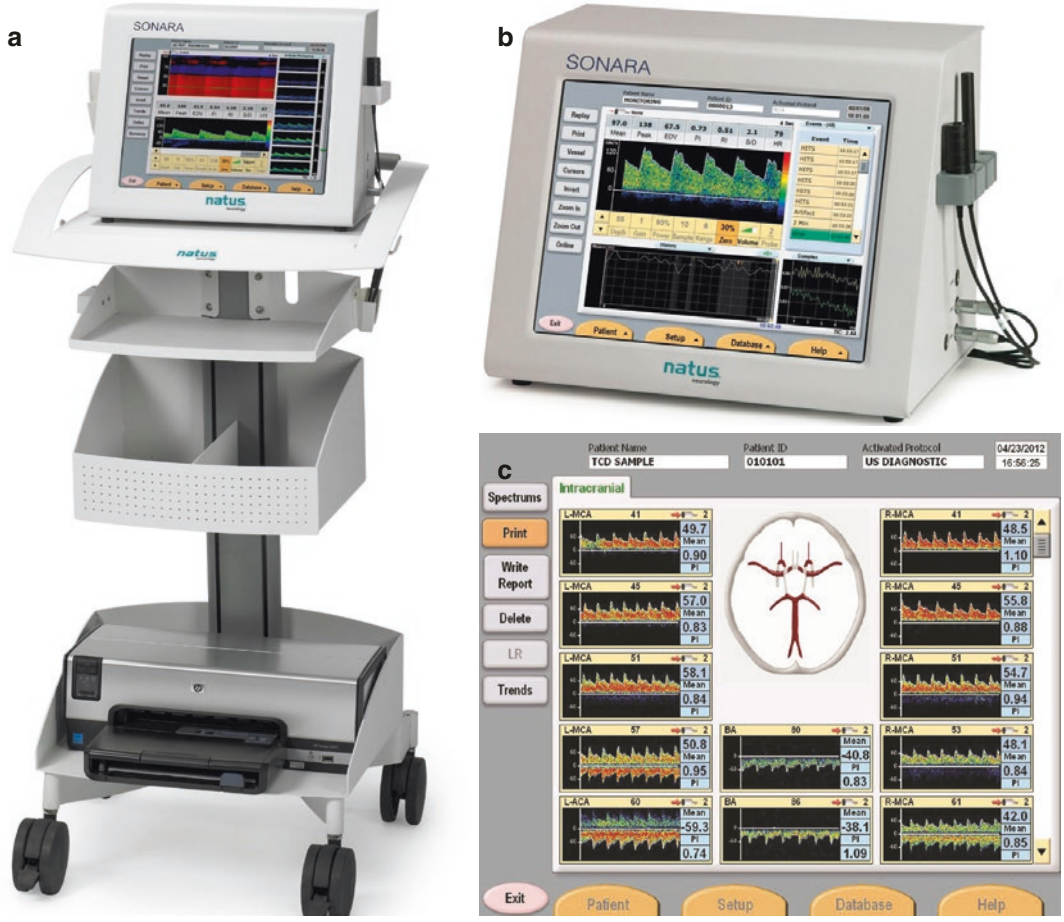

Fig. 9 The SONARA Transcranial Doppler (TCD) systems; (**a**): complete system; (**b**) the monitor; (**c**) the monitor panel of SONARA demonstrating Doppler waves on different arteries; (**d**) SONARA/TEK Digital TCD Module; (**e**) SONARA Doppler probes, **Published with kind permission of © Natus Neurology Incorporated, 2016. All Rights Reserved**

Fig. 9 (continued)

Jugular Venous Oxygen Saturation ($SjVO_2$)

Assessment of Jugular oxygen saturation goes back to more than 70 years ago; when the very first steps by Myerson et al. and Gibbs et al. have led gradually toward the current $SjVO_2$ monitoring. In 1942, Gibbs et al. described arterial and cerebral venous blood oxygen differences and some other biochemical differences; they studied 50 healthy young men (Gibbs EL et al. 1942). Then, in 1945, Gibbs et al. demonstrated that there is no difference in oxygen saturation between simultaneous right and left jugular bulbs (Gibbs EL and Gibbs 1945). Then, in 1963, Datsur et al. had a much more important finding: they described $SjVO_2$ as an "indirect surrogate indicator for global oxygenation of the cortex"; also, they had another main finding; they found $SjVO_2$ as an indicator for the balance between "Cerebral Blood Flow: CBF" and "Cerebral Metabolic Rate for oxygen: CMRO2" (Schell and Cole 2000; Chieregato et al. 2003).

What Does $SjVO_2$ Monitoring Show Us?

If we want to give a brief description; we can say: "$SjVO_2$ monitors the biochemistry profile of the venous blood draining each hemisphere." Of course, there is always some mixing between the right and left internal jugular vein, in such a way that venous drainage from each hemisphere is about 70% from the ipsilateral jugular vein and 30% from the contralateral vein; however, in most patients, the right internal jugular vein is the dominant drainage vein and this is why we usually monitor $SjVO_2$ through the right internal jugular vein. Although the right side is the dominant side, the mixing pattern between the right and left hemispheres is not always the same.

Though Gibbs and colleagues measured jugular venous samples instantaneously, currently available $SjVO_2$ monitors measure the following variables based on a continuous assay method:

- oxygen saturation in cerebral mixed venous blood; that is, blood draining total cerebral tissue,
- pH and PCO_2 in cerebral mixed venous blood,
- glucose and lactate levels in cerebral mixed venous blood.

Based on the above variables and simultaneous arterial levels, the monitor calculates the following:

- cerebral "***arterial-venous O2 difference***" or "A-V O_2 gradient: ΔA-VO_2" which is the difference between brain arterial and venous oxygen and it is a surrogate for CNS oxygen uptake; one should keep in mind that $SjVO_2$ is usually lower than simultaneous mixed venous

blood taken from a pulmonary artery catheter (i.e., systemic SvO_2); since O_2 consumption in brain tissue is higher than other tissues; so, mixed venous O_2 content of jugular vein is lower than systemic mixed venous O_2 content,
- cerebral "arterial-venous difference" for ***lactate***, ***pH,*** and ***PCO_2*** which demonstrates the metabolic state of brain tissue,
- cerebral "arterial-venous difference" for ***glucose***; increased gradient shows increased cerebral activity.

In other words, if cerebral tissue O_2 delivery cannot meet tissue O_2 demands, the cerebral tissue would not be well oxygenated, and the result will be an increased A-V gradient for oxygen. The increased ΔA-VO2 shows that inadequate brain tissue oxygenation leads to increased oxygen extraction from the arterial blood ending in a "widened difference" between arterial and mixed venous oxygen saturation (Yoshitani et al. 2005).

Usually, an increased A-V gradient for lactate, pH, and PCO_2 will be associated with increased "$\Delta A\text{-}VO_2$" which is evidence of the tendency to anaerobic metabolism and tissue oxygen deficiency. These parameters should be vigorously monitored in patients undergoing cardiopulmonary bypass; in cardiac surgery patients, some episodes need sophisticated care; like the rewarming period, patients undergoing antegrade cerebral perfusion, or patients with low flow pump states like "Deep Hypothermic Circulatory Arrest" (Shaaban Ali et al. 2001).

$SjVO_2$ Catheters and the Technique Used for Their Insertion

Currently, available $SjVO_2$ catheters use reflectance oximetry technology which is the technique used in pulmonary artery catheters; these catheters are usually one of the two models: 2 optical fibers or 3 optical fibers. In the 2 fiber model, light reflection to blood is through one fiber and the reflection of light is sent back to the *photosensor* of the monitor by the second fiber; patient hemoglobin should be given to the machine to calculate $SjVO_2$ a percentage of (Oxygenated Hb/total Hb). However, spectral absorption is used to calculate Hb concentration in 3 wavelengths catheters; so, in 3 wavelength monitors, real-time results of $SjVO_2$ are demonstrated.

In the older models of $SjVO_2$ "the ***conventional technique***" serial measurements of $SjVO_2$ are done which is associated with the limitation of "point checking of $SjVO_2$" mandating frequent sampling and serial measurement. Catheters with fiberoptic tips have removed the need for repeated sampling and give real-time data. Also, lateral neck rotation to either side will make erroneous or at least, biased results because the rotation of the head could affect the venous return and distort measurements (Howard et al. 1999; Schell and Cole 2000; Shaaban Ali et al. 2001).

Anatomic Approach

- usually, the approach is the same as used for the insertion of a central venous catheter (CVC) through the ***right internal jugular,***
- ***Seldinger*** technique is used needing a guidewire,
- although the jugular bulb is located just below the skull base, the preferred site for $SjVO_2$ cannulation is the same as CVC insertion: ***the anterior triangle,***
- the vein should be punctured in a ***cephalad direction***; also, the guidewire should be introduced cephalad; using Doppler sonography could be a feasible guide for locating the needle and the wire; however, in the past decades, X-ray has been used for documentation,
- if the patient is awake, a sense of pressure is felt in the skull base due to guidewire,
- the catheter is then inserted over the guidewire; Doppler sonography or an external sizer helps us determine the right location for the catheter tip,
- lateral or anteroposterior neck X-ray is the gold standard for verifying the location of the catheter tip; in X-ray results, we should look for the catheter tip to be around the mastoid process; a horizontal plane passes from the mastoid process, the first cervical spine and the inferior margin of the orbital rim,

- also, we could draw an imaginary line connecting the right and left mastoid processes and the catheter tip should be located just cephalad to this assumptive line,
- this technique has been used for ***both pediatric and adult patients,***
- the catheter tip should be as much as possible inside or at least, near the ***bulb of the jugular vein***; the optimum position is the roof of the jugular bulb which gives us the best $SjVO_2$ results,
- another simple and acceptable method (though not as exact as an X-ray) is to use the surface landmark for the jugular vein bulb which is 1 cm anterior and 1 cm below the mastoid process,
- the jugular bulb is located distal to the jugular foramen (jugular foramen is an anatomic window in the skull bone for emission of the jugular vein); this anatomic point is just located cephalad to the "common facial vein outlet,"
- before starting to measure $SjVO_2$, catheter calibration (both in vivo or in vitro) is necessary; this should be done based on manufacturer information,
- the catheter tip should not be displaced or entrapped into the jugular vein wall; otherwise, if the catheter tip is displaced or has moved more than 2 cm from the bulb of the jugular vein either cephalic or caudal, the results of $SjVO_2$ fall in the biased range of measurement and are not exact due to venous blood sample "contamination,"
- sampling speed should not exceed 2 mL/min, otherwise, there will be the risk of venous blood contamination because of blood mixing with extracranial venous blood and the result would be erroneous over-estimation of $SjVO_2$,

Contraindications for SjVO2 catheter insertion: the following causes are considered absolute contraindications for $SjVO_2$ catheter insertion:

- cervical spine injuries,
- bleeding diathesis,
- local trauma of the neck,
- local infection of the neck,

However, the following items are considered relative contraindications:

- impaired drainage of the cerebral veins,
- tracheostomy,

Complications of SjVO2 catheter: there are two main categories of complications related to $SjVO_2$ catheters:

- complications of $SjVO_2$ **catheter insertion procedure** (like tissue or arterial injuries); these are similar to central venous catheter insertion complications,
- complications of $SjVO_2$ catheter-related to the **residing catheter** (to be included: increased risk of thrombosis or infection).

Data interpretation by $SjVO_2$ monitor: the final $SjVO_2$ number depends on the following ratio:

$$CMRO_2 / CBF$$

$SjVO_2$ between 55 and 80% is considered normal; $SjVO_2 < 50\%$ is in the "desaturation domain" and $SjVO_2 > 80\%$ is in the "luxuriant saturation" domain (Schell and Cole 2000).

However, there is another approach for interpretation of SjVO2 data and that is the calculation of the **Arterial-jugular vein oxygen gradient (AjvDO2)**; this index is calculated using the following series of equations:

$$DO_2 = CBF \times CaO_2$$

$$CMRO_2 = CBF \times \left(CaO_2 - CjvO_2\right)$$

$$AjvDO_2 = CaO_2 - CjvO_2$$

in the above equations:

DO_2: Cerebral O_2 Delivery.
CBF: Cerebral Blood Flow.

$CMRO_2$: Cerebral Metabolic Rate for Oxygen (Cerebral O_2 Consumption).
CaO_2: Arterial O_2 Content.
$CjvO_2$: Jugular Vein O_2 Content.
$AjvDO_2$: Arterial-jugular vein Oxygen Gradient.

When solving the above three equations, we will have the following equation for $AjvDO_2$ which says:

$$AjvDO_2 = CaO_2 - CjvO_2$$

And finally, we reach this formula:

$$AjvDO_2 = CMRO_2 / CBF$$

Normally, $AjvDO_2$ is between 4 and 8 mLO_2/100 mL of blood. However, interpretation of abnormal $AjvDO_2$ has one of the two categories:

- $AjvDO_2 < 4$ mLO_2/100: shows a luxurious perfusion state with a resulting abundance of O_2 in venous blood (luxurious O_2 delivery).
- $AjvDO_2 > 8$ mLO_2/100: shows inadequate oxygen delivery to brain tissue, resulting in as much as possible oxygen extraction from blood with resulting widening of arterial and venous oxygen gradient (desaturation state).

Based on the two above approaches (the absolute value of $SjVO_2$ or $AjvDO_2$), a list of differential diagnoses could be seen in Table 3.

Limitations of Data Interpretation for $SjVO_2$ and Methods to Correct It

$SjVO_2$ is better to be defined as an "indirect surrogate index of global cerebral perfusion"; so, $SjVO_2$ could detect global cerebral ischemia but cannot detect exactly the location of the ischemic region in cerebral hemispheres; this definition implies that:

- $SjVO_2$ has high specificity,
- $SjVO_2$ has low sensitivity (in other words, $SjVO_2$ could),
- is affected by simultaneous hemoglobin concentration; saturation of the systemic arterial blood; core body temperature, fever, and/or hypothermia; level of CO_2 in the arterial blood; level of anesthesia and/or sedation.

The following items could be very useful guides for caring for the patient based on $SjVO_2$ results (Table 6) (Howard et al. 1999; Schell and Cole 2000; Shaaban Ali et al. 2001):

1. determine $SjVO_2$ state (desaturated State or luxuriant state),
2. if it is desaturated (i.e., $SjVO_2 < 50\%$) check a venous blood sample (VBG) analysis using a CVC catheter,
3. if VBG O_2 saturation is >50%, once again ***CALIBRATE*** $SjVO_2$ monitor,
4. correct the main determinants of **oxygen delivery,**
   - increase **hemoglobin** above 9 mg/mL,
   - correct **$PaCO_2$** above 30 Torrs (to reach 35–40),
   - increase **arterial oxygen saturation** (SaO_2) > 90%,
5. manipulate **intra-cranial hemodynamic status** to decrease intracranial pressure (ICP) < 20 and cerebral perfusion pressure (CPP) > 60 to have a CPP of at least 60–70 mmHg; of course, mean arterial pressure (MAP) should be controlled to be above the minimum perfusing level,
6. monitor and manipulate the underlying **metabolic state** of the brain (including temperature to prevent hypothermia, level of anesthesia to prevent wakefulness and inadequate anesthesia, EEG to prevent and treat any possibility of convulsion or electrical over-activity),
7. rule out arterial vasospasm by TCD.

Table 6 Differential diagnosis of cerebral perfusion state based on the absolute value of $SjVO_2$ and $AjvDO_2$ (Schell and Cole 2000)

Desaturated state ($SjVO_2 < 50\%$ or $AjvDO_2 > 8$)	Luxuriant state ($SjVO_2 > 80\%$ or $AjvDO_2 < 4$)
Decreases CBF • Head injury • Systemic hypotension • Increased ICP (e.g., brain edema or impaired cerebral venous return) • Arterial vasospasm • Hyperventilation/ hypocapnia • Thromboembolism • Arterial hypoxia (e.g., due to impaired ventilation due to lung pathology or ventilator problems, impaired hemoglobin oxygenation, or impaired transfer and delivery of oxygen to tissues including the brain)	**Increased CBF** • Hyperemia • Arteriovenous shunts
Increased $CMRO_2$ • Convulsion or seizure • Fever/hyperthermia • Inadequate anesthesia/ sedation level	**Decreased $CMRO_2$** • Anesthetic drugs depressing the level of brain function • Hypothermia • Brain death

Depth of Anesthesia and Sedation

Anesthesia level and sedation level are monitored using the Bispectral analysis index (BIS). During the perioperative period, the level of sedation/analgesia should be monitored to deliver adequate anesthesia/analgesia without over-administration. BIS has widespread use not only inside the operating room; but also, in the postoperative period, inside the intensive care unit, and for procedural sedation; especially in children in whom, clinical assessment of consciousness is not always an easy task. On the other hand, BIS could help us create appropriate documentation for patients undergoing anesthesia/sedation for the legal protection of the caregiver (Courtman et al. 2003; Johansen 2006; Lamas et al. 2009). BIS gives us a number that is categorized according to the following scale:

BIS level	Clinical state
>80	Awake
60–80	Sedation
40–60	Surgical anesthesia
<40	Deeply anesthetized

Evoked Potentials: Somatosensory Evoked Potential (SSEP), Motor Evoked Potential (MEP), Auditory Evoked Potential (AEP), and Visual Evoked Potential (VEP)

Evoked potentials provide real-time and objective data about the integrity of the nervous system which are both objective and reproducible data. For this purpose, the functional integrity of the central and peripheral nervous system throughout the neural circuits and neural pathways is monitored by different modalities of evoked potentials; including SSEP, MEP, VEP, AEP, and BAEP, discussed here. Three main modalities of evoked potentials are:

1. **Somatosensory Evoked Potential (SSEP)**: functional integrity of ascending pathways is monitored by SSEP, starting from peripheral receptors (median or ulnar nerve for upper extremity and posterior tibial nerve or peroneal nerve for lower extremity) going up to multiple spinal segments. Afterward, the neural pathway extends to the contralateral thalamus, finally ending in the cortical neurons. Visual Evoked Potential (VEP) is a subtype of SSEP monitoring visual stimuli as the sensory input.
2. **Motor Evoked Potential (MEP)** is the special modality of evoked potential for monitoring motor pathways. MEP monitors the neural process responding to the electrical motor stimuli starting from cortical neurons down to the related nuclei and corticospinal tracts and finally, reaching peripheral motor units.
3. **Visual Evoked Potential (VEP)** monitors the integrity and function of the visual neural pathway; starting from the retina, going through the optic nerve, optic chiasma, optic radiation, and finally, to the occipital cortex.

4. **Auditory Evoked Potential (AEP)** objectively monitors the neural pathway involved in hearing; this pathway starts from the cochlea, goes to the ear, and reaches the auditory nerve (eighth cranial nerve). The final destination of this pathway is the brainstem, the related brain ganglia, and finally related cortical areas. In AEP, the first milliseconds monitor the "brainstem" function which is part of the auditory pathway; this part of AEP is called brainstem auditory evoked response (BAEP).

SSEP, MEP, VEP, AEP, and BAEP are frequently used in clinical practice including in the perioperative period of pediatric cardiac surgery patients; with the following items as the main indications for their use:

- CNS monitoring during therapeutic hypothermia; meanwhile EEG becomes but evoked potentials function well to monitor CNS integrity.
- CNS monitoring in patients with unstable hemodynamics, deep sedation, altered consciousness states (Keenan et al. 1987; Burrows et al. 1990; Rosenblatt 1999; Freye 2005; Kunihara et al. 2007; Sloan and Jameson 2007).

The main differences between EEG and evoked potentials could be summarized as:

- lower voltage amplitude in evoked potentials compared to EEG.
- EEG is the demonstration of the spontaneous electrical activity of cerebral cortical neurons while evoked potentials are the neurologic response to a variety of stimuli by the monitor (sensory or motor).
- EEG monitors the cerebral cortex exclusively; while evoked potentials could monitor the cerebral cortex, deeper nuclei, parts of the brain stem; spinal cord, and peripheral nerves.
- functional integrity of the nervous system is checked by evoked potentials even during deep anesthesia or therapeutic hypothermia; in these latter clinical conditions, EEG may be flat while evoked potentials still work.

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Perioperative Respiratory Monitoring in Congenital Heart Disease Patients

Stacey Marr and Ali Dabbagh

Abstract

Respiratory monitoring is one of the most important tasks in medicine; especially in critically ill patients. However, when a patient, especially a child undergoes some complex surgeries like surgery for congenital heart diseases, respiratory monitoring is much more stressed; though not such a simple task. Respiratory monitoring in congenital heart diseases starts from history taking and clinical examination to different ancillary assessment methods, including pulse oximetry, capnography, blood gas analysis, monitoring of the ventilator and mechanical ventilator support systems, and other technologies. Though we are in the era of emerging technologies, basic clinical principles are still the cornerstone of respiratory assessment. Meanwhile, age-matched trends should be considered in the assessments.

Keywords

Respiratory monitoring · Congenital heart diseases · Pulse oximetry · Capnography Blood gas analysis

Introduction

There is no doubt that respiratory function is one of the main functions of the human being. Respiratory monitoring is one of the most important tasks in medicine; especially in critically ill patients. However, when a patient, especially a child undergoes some complex surgeries like surgery for congenital heart diseases, respiratory monitoring is much more stressed; however, this is not such a simple task (Brochard et al. 2012; Egbuta and Mason 2020; Bosch et al. 2021). In this chapter, we will discuss the main modalities for respiratory monitoring; starting with clinical assessment, then a brief discussion on the monitoring devices.

Clinical Assessment

Clinical assessment is of great importance when assessing a child after cardiac surgery (Gazit et al. 2010; Rossol et al. 2020). As with all monitoring, assessment parameters need to be taken in

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the context of the child, i.e., what is "normal" for one child will not necessarily be "normal" for another (Sivarajan and Bohn 2011). Recent works by Bonafide et al. have highlighted that the normal range for vital signs among hospitalized children can differ significantly from traditional reference ranges (Bonafide et al. 2013). A clinical assessment of a child will require using the four key skills of inspection, auscultation, palpation, and percussion.

Inspection

This skill is useful to assess respiratory rate and pattern as well as the work of breathing, color, and emotional state of the child. This portion of the assessment requires the assessor to look at the *rate*, *pattern*, and *work* of *breathing* (WOB).

Respiratory Rate and Other Vital Signs

Normal respiratory rates for infants and children are listed below, however as previously discussed hospitalized children frequently do not fall within these parameters (Bonafide et al. 2013; Herbert et al. 2020; Park and Khattar 2021). Furthermore, children with congestive heart failure will typically have a significantly faster respiratory rate than their unaffected peers; so, an age adjustment measurement of respiratory rate is needed (Table 1). When assessing the rate in children after cardiac surgery it will be more important to review the trend of the rate rather than a single event; i.e., is the child becoming more tachypneic? A very slow respiratory rate in infants and children is a sign of imminent respiratory arrest or overdosing with narcotic agents (Davis et al. 2009; Sweet et al. 2017). Also, when assessing the respiratory rate, it is often needed to assess the heart rate and blood pressure; since the cardiopulmonary interactions lead to clear clinical correlations between these clinical assessments; however, the latter assessments also need age adjustment (Tables 2 and 3).

Table 1 Normal age-matched respiratory rates (Davis et al. 2009; Fleming et al. 2011; Bonafide et al. 2013; Elder et al. 2013; Ross and Rosen 2014; McCollum et al. 2015; Auten et al. 2016; Herbert et al. 2020)

Age	Normal rate: 50th percentile (5–95 percentile)
0–3 months	41 (27–62)
3–6 months	38 (25–58)
6–9 months	35 (23–54)
9–12 months	33 (22–51)
1–2 years	31 (22–43)
2–3 years	27 (18–42)
3–4 years	25 (18–40)
4–6 years	24 (17–37)
6–12 years	22 (15–35)
12–15 years	19 (13–28)
15–18 years	18 (13–26)

The Pattern of Breathing

Infants and children are nasal breathers and the ratio of inspiration to expiration is 1:2 or 1:3 in normal breathing. The regularity of breathing is particularly important to assess as apnea (cessation of breathing for 20 s or more) is a sign of significant respiratory distress in infants and neonates, though neonates will often have short periods of apnea, referred to as periodic breathing and this is normal as long as it is not associated with a change in color or desaturation. On inspiration thoracic expansion and abdominal bulging ought to be seen in infants and young children and loss of this synchrony of movement is referred to as "see-saw" breathing and is an abnormal pattern in this age group. Depth of breathing is also an important measure of the effectiveness of respiration as shallow breathing leads to relatively poor gas exchange (Saraya et al. 2016; Pramono et al. 2017; Sweet et al. 2017; Chakkarapani et al. 2020; Bianco et al. 2021; Delecaris et al. 2021; Erickson et al. 2021).

Table 2 Normal range of blood pressure in *BOYS* with special focus on "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" of the "National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents"

	DBP (mmHg)		SBP (mmHg)		MAP (mmHg)	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	34–39	54–58	80–89	98–106	49–55	69–75
2	39–44	59–63	84–92	101–110	54–60	73–79
3	44–48	63–67	86–95	104–112	58–64	77–82
4	47–52	66–71	88–97	106–115	61–67	79–86
5	50–55	69–74	90–98	108–116	63–69	82–88
6	53–57	72–76	91–100	109–117	66–71	84–90
7	55–59	74–78	92–101	110–119	67–73	86–92
8	56–61	75–80	94–102	111–120	69–75	87–93
9	57–62	76–81	95–104	113–121	70–76	88–94
10	58–63	77–82	97–106	115–123	71–77	90–96
11	59–63	78–82	99–107	117–125	72–78	91–97
12	59–64	78–83	101–110	119–127	73–79	92–98
13	60–64	79–83	104–112	121–130	75–80	93–99
14	60–65	80–84	106–115	124–132	76–82	95–100
15	61–66	81–85	109–117	126–135	77–83	96–102
16	63–67	82–87	111–120	129–137	79–85	98–104
17	65–70	84–89	114–122	131–140	81–87	100–106

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Table 3 Normal range of blood pressure in *GIRLS* with special focus on "The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents" of the "National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents"

	DBP (mmHg)		SBP (mmHg)		MAP (mmHg)	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	38–42	56–60	83–90	100–107	53–58	71–76
2	43–47	61–65	85–91	102–109	57–62	75–80
3	47–51	65–69	86–93	104–110	60–66	78–83
4	50–54	68–72	88–94	105–112	63–67	80–85
5	52–56	70–74	89–96	106–114	64–69	82–87
6	54–58	72–76	91–98	108–115	66–71	84–89
7	55–59	73–77	92–101	110–119	67–73	85–91
8	57–60	75–78	94–102	111–120	69–74	87–92
9	58–61	76–79	95–104	113–121	70–75	88–93
10	59–62	77–80	97–106	115–123	72–77	90–94
11	60–63	78–81	99–107	117–125	73–78	91–96
12	61–64	79–82	102–109	119–126	75–79	92–97
13	62–65	80–83	104–110	121–128	76–80	94–98
14	63–66	81–84	106–112	123–129	77–81	95–99
15	64–67	82–85	107–113	124–131	78–82	96–100
16	64–68	82–86	108–114	125–132	79–83	96–101
17	64–68	82–86	108–115	125–132	81–84	96–101

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Work of Breathing (WOB)

The respiratory rate and pattern will give some idea of the work associated with breathing; however, describing the work of breathing in terms of the use of accessory muscles and the presence of recession is a clearer indication of respiratory function.

Nasal Flaring

A widening of the nostrils while breathing is more commonly seen in infants and young children and is a very subtle sign of respiratory distress and is easily missed by practitioners (Fig. 1).

Recession

Infants and children have a very pliable rib cage and when respiratory rate effort is increased some in-drawing or retraction can be seen along the costal margins where the diaphragm attaches (subcostal recession) or between the ribs (intercostal recession) (Challands and Brooks 2019; Park and Khattar 2021). In very small infants the whole sternum may be drawn in (sternal recession) and recession above the sternum, between the clavicles, is described as a tracheal tug. As a child grows the ribcage becomes more rigid and recession will rarely be seen, though the recession in an older child (5+ years) is a sign of significant respiratory distress (Fig. 1).

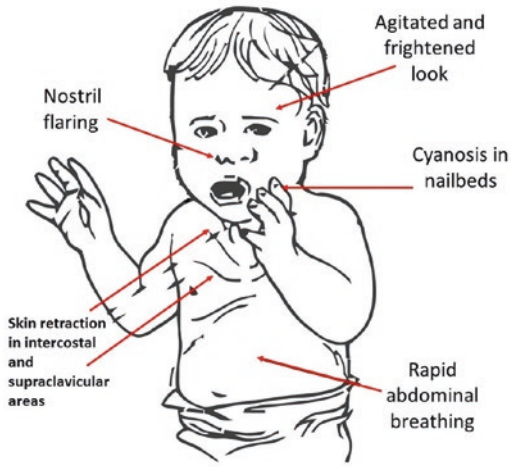

Fig. 1 A child with respiratory distress

Accessory Muscle Use

In respiratory distress a child may use accessory muscles to aid breathing, these muscles are used to increase the size of the thoracic cavity on inspiration and the use of these muscles is a pre-terminal sign in infants and children as they will tire easily and have a little respiratory reserve. Head bobbing in infants is only seen as the infant uses the sternomastoid muscle to aid breathing (Fig. 1).

Skin Color

The assessment of skin color in children with congenital heart disease is often a complex process, as children with reduced pulmonary blood flow will appear cyanosed without respiratory distress, and children with congestive cardiac failure will appear pale. In normal children the presence of cyanosis is considered to be a severe sign of respiratory distress, however, for children with congenital heart disease, this may be normal. The assessment of color should be combined with activity in an awake child. A child or infant who has cyanosis from a respiratory cause; i.e., an acute reduction in available oxygen, will have an altered state of consciousness whereas a child who has cyanosis from their cardiac lesion will most likely be sitting and playing without signs of respiratory distress. In the older child, the presence of clubbing of the fingers or toes will indicate longer-term cyanosis.

Auscultation

Auscultation also involves listening without the stethoscope to hear respiratory noises and then using the stethoscope to hear breath sounds (Bohadana et al. 2014). Auscultation is a skill that develops over time and care ought to be taken to

ensure the sound heard is coming from the child and not the equipment; also, an orderly performed pattern should be adopted for auscultation; both anterior side and posterior side (Fig. 2).

Respiratory Sounds

Breath sounds are caused by vibrations against the airway walls by the turbulence of air as it passes through the airways (Bohadana et al. 2014). The sounds are produced in the large airways and transmitted via lung tissue and rib cage to the surface and can be heard with a stethoscope.

The sounds heard during auscultation should be compared one side to the other and reported in terms of (Kim et al. 2021):

1. Sound: Describe the noise heard, i.e., crackles, wheeze, stridor.
2. Intensity: this refers to the pitch of the sound high (soft) or low (loud).
3. Timing: does the sound occur on inspiration or expiration or is it Biphasic?
4. Quality: is it continuous or intermittent?

Normal Breath Sounds

Here, the main categories of normal breath sounds are presented; their classification is both physiologically and anatomically related (Bohadana et al. 2020; Kim et al. 2021). If any of the normal breath sounds are heard in unrelated anatomical locations, then they should be considered *abnormal breath sounds*.

- *Bronchial sounds* should be heard in the large airways—they are loud high pitched sounds heard on inspiration and expiration. The presence of these sounds over the lung fields is an abnormal finding suggestive of consolidation or collapse of a lobe.
- *Vesicular sounds* are heard in the smaller airways and periphery of the lung field. They should be quiet and low pitched sounds; an increase in the intensity of these sounds can also suggest pulmonary consolidation.
- *Bronchovesicular sounds* consist of a full inspiratory sound and a softer shortened expiratory sound, they are best heard in the hilar region; an increase in the intensity of these sounds can indicate a consolidation.

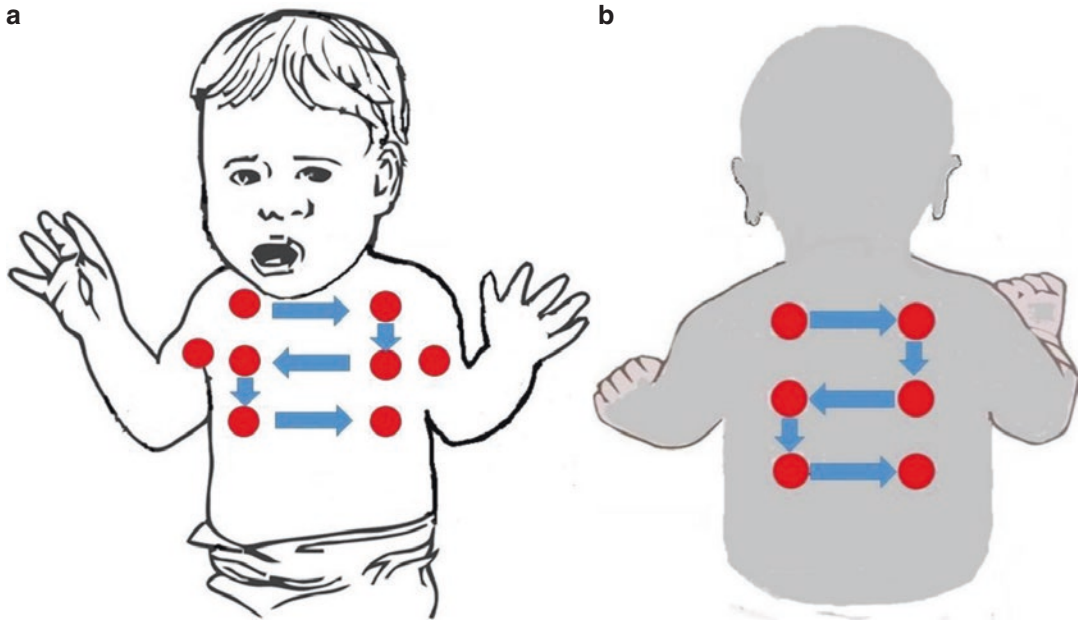

Fig. 2 Orderly performed auscultation. (**a**) Anterior Chest; from top to down and also, including both armpits; (**b**) Posterior Chest, from top to down

Adventitious or Abnormal Sounds

These are the sounds that are not heard in any lung field in physiologic conditions; besides, as described above, normal breath sounds heard in unrelated anatomical locations are considered *abnormal breath sounds* (Aviles-Solis et al. 2017, 2019, 2020).

- *Stridor*: a loud monophonic wheezing sound usually heard in the extrathoracic airways, it is associated with laryngeal or tracheal obstruction and post-extubation stridor is common in children with Down's syndrome. The sound is initially heard on inspiration and as it worsens the sound will become biphasic and then silent (Celmina and Paule 2018).
- *Wheeze*: a high-pitched musical sound, most commonly heard on expiration and is often associated with a prolonged expiratory phase. This sound is produced by the high-velocity flow of air through a restricted airway lumen and indicates intra-thoracic airway obstruction. This sound is initially heard on expiration but as the condition worsens it will become biphasic and eventually silent. Children with pulmonary edema or congestive heart failure may present with an inspiratory wheeze referred to as a "cardiac wheeze."
- *Crackles:* inspiratory high pitched sounds like paper or hair being rubbed together, they are discontinuous, sounds that originate within the airways. They are heard when an obstructed airway suddenly opens and the pressures on either side of the obstruction suddenly equilibrate resulting in transient, distinct vibrations in the airway wall. The dynamic airway obstruction can be caused by either accumulation of secretions within the airway lumen or by airway collapse caused by pressure from inflammation or edema in surrounding pulmonary tissue.
- *Grunting*: This sound is heard when a child is maintaining auto peep against a closed glottis.

Palpation

This skill has limited usefulness in infants though can be used to discover skeletal deformities, or crepitus (crackles). Palpation of the thorax ought to give information on the position of the trachea, symmetry of chest movement, voice/breath sounds, and the presence of subcutaneous emphysema (Reyes et al. 2021).

Percussion

This skill is essential to performing an accurate respiratory assessment of infants and children. Percussion is performed by placing the middle finger of the non-dominant hand flat on the patient's body and then tapping the distal joint with the middle finger of another hand, this can be a difficult skill to master and will take time and practice. Percussion is used to determine the presence of air (high resonance on percussion), fluid, or masses (dull resonance on percussion) within the thorax (Pasterkamp et al. 1997; Oliveira and Marques 2014; Davis and Murray 2016; Reyes et al. 2021). In infants, this skill may be the only way to determine the presence of a pneumothorax or effusion as breath sounds can be misleading in this age group as sounds are transmitted across the relatively thin-walled chest cavity.

Cardiopulmonary Interactions

The ability to perform and report an accurate clinical assessment of the respiratory system in children following cardiac surgery is imperative to aid management decisions. Most children with cardiac disease have few primary pulmonary problems and thus a respiratory assessment cannot be taken in isolation from a good cardiovascular assessment nor the absence of knowledge about cardiopulmonary interactions (Shekerdemian and Bohn 1999; Agha et al. 2014).

Cardiopulmonary interaction is a term that describes the inseparable connection between the heart and the lungs as they work to meet the tissue's oxygen demand. Any alteration or dysfunction in one system will have consequences for the other system and often intensive care interventions, which are aimed to improve the function of one system, will have a deleterious effect on another. The peripheral venous system is extrathoracic and therefore at atmospheric pressure (Shekerdemian and Bohn 1999; Bronicki and Anas 2009; Pinsky 2018).

The pulmonary circulation and heart are intrathoracic and are influenced by changes in intrathoracic pressure. During normal respiration, the muscles of respiration generate a negative intrathoracic pressure, the negative pressure generated by deep inspiration maximizes the pressure gradient between the peripheral venous system and the right atrium and facilitates Right atrial filling and thus preload. On the other hand, the thoracic aorta is located within the thoracic cavity and is subject to changes in pleural pressures. The difference between the pressure within the aorta and the pleural pressure is referred to as transmural pressure. In normal respiration, the pleural pressure falls during inspiration and thus increases the transmural pressure and consequently left ventricular afterload. The application of positive pressure ventilation alters this delicate balance and can have serious consequences for children after cardiac surgery (Pinsky 1997; Thomson 1997; Tregay et al. 2016; Magder 2018; Mahmood and Pinsky 2018).

Respiratory Monitoring Adjuncts

There are many new techniques for respiratory monitoring that have become available in recent years and the appropriate use of available monitoring procedures can improve patient safety and outcomes in intensive care (Brochard et al. 2012). In the pediatric context, some of the newer modalities are of limited usefulness or are impractical for use with our population therefore this chapter will limit this discussion to pulse oximetry and capnometry/capnography (Rimensberger 2009a, b; Rettig et al. 2015; Chen et al. 2016).

Pulse Oximetry

This is widely used in pediatric intensive care and by anesthetists during surgical procedures. It is a measure of the age of hemoglobin saturated with oxygen which is estimated by the rate of absorption of two different wavelengths of light (Sivarajan and Bohn 2011; Röttgering et al. 2021). The use of this measurement tool is widespread and one of the advantages of its use is that most practitioners are familiar with the equipment used and the significance of the results. It is also very useful as an early warning signal and will reduce the frequency of arterial blood gas sampling (Brochard et al. 2012). The disadvantages of this measurement are that it cannot distinguish between normal hemoglobin, carboxyhemoglobin, and methemoglobin, it loses sensitivity at lower saturation levels and movement and artifact will affect the results seen; this is a major drawback in pediatric cardiac ICU where patients are often restless and also, a considerable number of patients have cyanotic cardiac diseases with low arterial oxygen levels (Jubran 2015; Arigliani et al. 2020; Röttgering et al. 2021). The other point to note is that this device will measure the age of hemoglobin saturated with oxygen but will not distinguish a low oxygen-carrying capacity in the presence of acute anemia—for example, a child may be received from the operating room with a measured saturation of 100% and a Hb of 14 g/dL if that child is bleeding and the Hb falls to 7 g/dL the pulse oximeter will likely still measure the saturation as 100% even though the oxygen-carrying capacity of the blood has reduced by half. The probe must fit the child as poorly fitting probes will provide inaccurate data; observing a good correlation between the heart rate measured on electrocardiogram (ECG) and the pulse rate mea-

sured by the pulse oximeter will aid in determining whether the probe is reading accurately or not (Torp et al. 2021). As with any single parameter it cannot be taken in isolation and recording the saturations hourly, and observing for a trend will be more useful in aiding clinical decision making.

Capnography and Capnometry

The measurement of end tidal CO_2 ($ETCO_2$) has been available for more than 30 years and used in adult intensive care units for many of those years. Capnography works by capturing exhaled air and redirecting it into the capnography device. The air then passes between a light and a detector that measures how much light is shining on it. As the concentration of CO_2 increases, more light is absorbed by the CO_2 and less light is transmitted onto the detector plate. An initial reluctance to use this measure in children was related to the large device size and consequent increase in dead space and the lack of cuffed tubes used in this age group. However, as devices have become smaller and more accurate this reluctance has faded and the use of end tidal CO_2 on ventilated patients in the ICU has become the "gold standard" of care. The information which can be derived from $ETCO_2$ are changes in alveolar ventilation; confirmation of endotracheal tube placement; the degree of right to left intracardiac shunt; change in pulmonary blood flow; and effectiveness of cardiopulmonary resuscitation. This adjunct can be used solely to measure the graphical representation of expired CO_2 (capnography), provide a number for end-expiratory CO_2 (capnometry), or more usefully in cardiac patients to observe differences in $PaCO_2$ and $ETCO_2$ (Fig. 3). In cases of systemic to pulmonary artery shunt monitoring the difference between $ETCO_2$ and $PaCO_2$ will provide essential information regarding shunt patency—if the shunt were to become blocked then the $PaCO_2$ would rise with a consequent fall in the $ETCO_2$ indicating reduced pulmonary blood flow (Sivarajan et al. 2008, 2011; Clarizia et al. 2011; Sivarajan and Bohn 2011).

The ultimate reading at the end of step 3 is the end tidal CO_2 reading, which is depicted on the monitor panel page.

Blood Gas Analysis

Though among invasive monitoring modalities, arterial blood gas analysis is considered a basic monitoring approach in the assessment of the

Fig. 3 Elements of a capnography waveform: (*0*) Inspiratory Downstroke. (*1*) Respiratory Baseline. (*2*) Expiratory Upstroke. (*3*) Alveolar Plateau

appropriateness of the respiratory system function in critically ill patients. Frequent sampling might lead to inadvertent blood loss; also, repeated sampling (either using an arterial line or intermittent arterial puncture) is another disadvantage of arterial blood gas analysis. Interpretation of the results needs both knowledge and experience. Despite the latter shortcomings, paramount invaluable information is obtained from this method that other alternative methods, often cannot be a good competitor for it, especially in the evaluation of the oxygenation, ventilation, and metabolic states (Brochard et al. 2012; Donoso et al. 2016). Detailed discussion on the arterial blood gas analysis in the perioperative period is presented in "Postoperative Renal Management, Fluid/Electrolyte Management, and Acid-Base Disorders."

Monitoring the Ventilator and Mechanical Ventilator Support Systems

Several main items should be considered in respiratory monitoring during invasive or noninvasive assisted ventilation

- Respiratory flow.
- Resistance of the airway.
- Airway pressure.

However, there are many indices used to monitor the three latter items, including but not limited to the following:

Ventilator pressures; ventilator traces; respiratory mechanics' indices; compliance and resistance of the airways; pressure/volume curves and pressure/flow monitoring; work of breathing; occlusion pressure ($P_{0.1}$); diaphragmatic function; work of breathing; pressure-time product; extravascular lung water, etc. A full description of the latter indices is discussed in the mechanical ventilation references; however, a brief discussion is presented in "Postoperative Respiratory Management in Congenital Cardiac Surgical Patients."

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Perioperative Coagulation Monitoring in Congenital Heart Disease Patients

Antonio Pérez Ferrer and Pablo Motta

Abstract

Bleeding after cardiac surgery is a common and severe complication leading to transfusion of multiple blood products and increased morbidity and mortality. Young age, low weight, polycythemia, profound hypothermia, and complex cardiac surgery are risk factors for severe bleeding. In addition, we need to account for the growing use of drugs that affect platelet aggregation and coagulation, which could increase the bleeding risk if not managed correctly.

Point-of-Care (POC) testing allows monitoring of one of the most problematic aspects that concern the health care providers when faced with surgical procedures, the hemostasis. POC bedside tests allow operating room or the intensive care diagnoses of coagulopathy of diverse etiology. Evidence-based algorithms integrate POC testing as one of the essential mechanisms to limit blood product transfusion, adverse events and allow goal-directed therapy.

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Keywords

Blood coagulation · Point-of-Care testing · Thromboelastography · Cardiac surgery procedures · Pediatrics

Introduction

Hemorrhage is a common problem during and after congenital heart surgery that challenges surgeons and anesthesiologists. Young age, low weight, polycythemia, profound hypothermia, and complex cardiac surgery are risk factors for severe bleeding (Miller et al. 1997a; Williams et al. 1999; Szekely et al. 2009). In addition, we need to account for the growing use of drugs that affect platelet aggregation and coagulation, which could increase the bleeding risk if not managed correctly. Bleeding and transfusion of blood components associated with a dose-dependent increase in postoperatively morbi-mortality (Willems et al. 2010; Wolf et al. 2014; Agarwal et al. 2015a).

During the preoperative evaluation, the surgeon and the anesthesiologist should estimate the bleeding risk (congenital or acquired disease) and plan accordingly. In addition, they should be able to diagnose and treat bleeding during and after surgery. Thus, the approach to perioperative bleeding should be multidisciplinary, including surgery, anesthesia, and nursing since it is a dynamic process triggered by surgery. Still, if not

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addressed early, it will turn into coagulopathy due to factors depletion.

In any bleeding, it is imperative to diagnose the triggering factors. In addition, it is essential to monitor coagulation adequately to differentiate between surgical and medical causes of bleeding, allowing a directed therapy. Perioperative bleeding is not a straightforward phenomenon like hemophilia (one missing factor can be easily replaceable). It is dynamic multifactorial event caused by previous exposure to the anticoagulant, antiplatelets, loss of coagulating factors, cellular elements during surgery, and in some situations developing hyperfibrinolysis. Due to this fact it is crucial to monitor the cause of coagulopathy and guide its therapy promptly (Nakayama et al. 2015).

Pediatric Hemostasis

Hemostasis is a multifaceted physiological process. There is a complex balance between the opposite mechanism of coagulation and anticoagulation, which protects the vascular system from uncontrolled bleeding or excessive clotting. There are three phases in the coagulation process. Under normal conditions, interact together to produce a clot in the injury area, preserving the flow to the rest of the body. The first phase is the primary hemostasis, where the platelets form thrombi when faced with the damaged endothelium. Next, secondary hemostasis or coagulation is when fibrinogen transforms to fibrin, in which the clot reinforces the initial thrombi. Lastly, when the clot degrades, the tertiary phase of hemostasis is no longer needed (fibrinolysis). During the last few years, significant advances made in the knowledge of the physiology of coagulation shifted from the classic cascade model of coagulation based on laboratory testing (prothrombin time and activated partial thromboplastin time) to a different cellular model of coagulation (Hoffman and Monroe 2001). In this model, tissue factor–FVIIA has a crucial role with other cellular elements which carry tissue factor and platelets whose surface generates large quantities of thrombin which converts fibrinogen into fibrin. Coagulation's most significant maturation changes occur during the first six-month of life, but they develop through infancy (Andrew et al. 1992; Miller et al. 1997a, b). The maternal coagulation factors (cF) do not cross the placenta, so the number of neonatal factors is due to synthesis, which starts in the fifth week of life and peaks on the eleventh week.

Table 1 Neonatal hematologic system

• Compensates the reduction of oxygen-carrying capacity by the anemia by increasing cardiac output (limited response)
• Fetal adaption to low intrauterine oxygen tension increases hematocrit through Hb F (70% in the neonate). Transfusion increases the risk of retrolental fibroplasia and necrotizing enterocolitis
• More catabolism linked to decreased erythropoietin production: Infant physiologic anemia (8–12 weeks of life)
• Immunosuppression state: Maternal antibodies could create a graft versus host disease (GVHD) and increase the risk for infection (CMV)
• Risk of anemia due to multiple blood draws. Limit the volume and number of draws
• Higher susceptibility to citrate intoxication
• Efforts need to be made to decrease the number of transfusions and exposure to donors (use of pediatric units)
• There is a reduction in the coagulation factors vitamin K dependent, contact factors, and natural coagulation inhibitors
• Hypofibrinolysis and primary hemostasis are enhanced besides an impaired platelet function
• Hemostatic balance is adequate besides prolonged cephalin time during the first 3–6 months of life

Even though all the components of the hemostatic system are present at birth, the neonatal hematologic system has peculiarities described in Table 1.

Comparison Between Neonatal and Adult Hemostasis

There are qualitative and quantitative differences between neonates and adults (see Table 2).

Due to these developmental differences, activated partial thromboplastin time (aPTT) prolongs during the first 3 months of life without increasing the risk of bleeding. Despite this, newborns have a good balance between procoagu-

Table 2 Comparison between neonatal and adult hemostasis

Component	Neonatal function	Effect on the hemostasis
Coagulation factors	↓F II, VII, IX, XI, XII ± Fibrinogen, F V ↑ F VIII	↓ Thrombin generation
Primary hemostasis	↑VWF ↓ Platelet function	↑ Primary hemostasis
Fibrinolysis	↓ Plasminogen, t-PA, y α_2 antiplasmin ↑PAI	Hypofibrinolysis
Natural coagulation inhibitors	↓AT, proteins C y S	↓ Inhibition capacity of activated coagulation proteins

F factor, *VWF* Von Willebrand factor, *t-PA* tissue plasminogen activator, *PAI* plasminogen activator inhibitor, *AT* antithrombin

lants and natural anticoagulants that allow surgery without increased bleeding risk. In addition, another coagulation test, like bleeding time, is decreased while the thromboelastogram shows a hypercoagulable trace with shortening of the reaction time (Miller et al. 1997b).

Congenital Heart Disease and Coagulation

Congenital heart disease (CHD) is associated with coagulation anomalies. In addition, platelets turnover anomalies with increased peripheral destruction and a higher rate of young "sticky" platelets significantly reduce the large multimer von Willebrand factor levels that improve post-corrective surgery.

Cyanotic heart disease has been associated with coagulation defects. The increased red cells production secondary to chronic hypoxemia decreases platelet synthesis in an inverse related ratio. In addition, the platelet lifespan is shorter with decreased adhesion and aggregation properties. Recently, Gertler et al. (2014), in a study of platelet function in cyanotic pediatric patients by multiple electrode aggregometry, showed that there was no clinically significant effect of cyanosis on the baseline and perioperative platelet function, chest tube drains, and the number of exposures to blood products. The authors concluded that children under 1 year of age do not require a different approach regarding platelet transfusions, independent of cyanosis.

Low cardiac output and liver congestion can decrease the production of coagulation factors, especially the vitamin K-dependent ones (II, VII, IX, and X). In addition, the levels of fibrinogen, anti-thrombin III (ATIII), factors V and VII, and proteins C and S levels are reduced in hypoplastic left heart syndrome (after first stage palliation. Controversy exists regarding the hypocoagulable state in pediatric patients with CHD. Is it real or just a technical artifact from a traditional coagulation test and thromboelastogram (Spiezia et al. 2013). The quantity of plasma, coagulation factors, and anticoagulant proteins in these patients decreases about polycythemia. The reduction of pro and anticoagulant factors in CHD increases the incidence of thromboembolic and bleeding complications. Due to this fact, this patient population requires heightened vigilance and proactive therapy (Eaton and Iannoli 2011).

Clinical Evaluation and Preoperative Laboratory Testing

The most common laboratory testing used to evaluate coagulation in our patients is the PT, INR, aPTT, fibrinogen, and platelet count. During the perioperative period, the use of these testing has been questioned since they are not predictive of hemorrhage (Dzik 2004; Chee et al. 2008; Samkova et al. 2012). The abnormal results rate of "traditional" testing is 0.4–46% which changes patient management in only 0–7% and detects complications in only 0–8% of the patients. There is no evidence in adult and pediatric medical literature that this preoperative testing improves patient outcomes. In addition, 64% of PT and 94% of aPTT of interoperative measurements in major pediatric surgery were outside the reference range.

In comparison, impaired CT was observed in 13% and 6.3% of EXTEM and INTEM ROTEM

clotting times. The correlation between PT and aPTT to EXTEM and INTEM was poor. Therefore, the recommended thresholds for PT and aPTT might overestimate the need for coagulation therapy (Haas et al. 2012). A well-structured questionnaire about bleeding history has a better predictive value for perioperative hemorrhage than any coagulation testing (Chee et al. 2008).

Coagulopathy and Cardiac Bypass

Cardiac surgery is one of the surgical procedures that affect more the hemostatic milieu. Patients with cardiomyopathy are hypercoagulable and require anticoagulant and antiplatelet therapy. This therapy must be held in the preoperative period. Following cardiopulmonary bypass (CPB), the balance shifts to coagulopathy. Recent advances in CPB circuits reduce the inflammatory activation, but they remain profoundly non-physiologic. High-dose heparin avoids thrombosis of the CPB circuit, but a low level of intravascular and intra-circuit coagulation continues through the bypass. The exposure of blood to the negatively charged surfaces of the CPB circuit triggers fibrinogen binding to the circuit, platelet, and coagulation activation (Via Factor XII). Once the platelets have been activated, they are not functional for the postoperative hemostasis. The extrinsic pathway is activated through the release of tissue factors during surgery. Both coagulation pathways activate thrombin with thrombotic and anti-thrombotic effects (Eaton and Iannoli 2011). The mechanical impact caused by the pump turbulence damages platelets and consumes coagulating factors. In addition, the hemodilution effect by the CPB priming on the coagulating factors and platelets produces a hypocoagulable state upon CPB wean and through the postoperative period. In 5–7% of the CPB runs, the endothelium reacts to the surgical trauma releasing TPA (Tissue Plasminogen Activator), which in a hypocoagulable state causes a state of primary fibrinolysis. The activation of the coagulation by the CPB circuit, microembolic production, and tissue debris make the patient prone to a hypercoagulable condition even after heparin reversal. CPB is a profoundly proinflammatory state with activation of multiple inflammatory humoral (e.g., interleukins and complement) and cellular mediators (e.g., monocytes and neutrophils). The inflammatory system and coagulation interact at many different levels, by reducing inflammation which reduces the activation of coagulation, and vice versa (Cappabianca et al. 2011).

Monitoring of Coagulation

Laboratory-Based Coagulation Test

As previously stated, the use of traditional laboratory testing has been questioned since it is not predictive of perioperative bleeding during the perioperative period. Furthermore, standardized testing in the perioperative period has been examined due to the slow turnover (45–60 min). By the time the results are back, the patient situation may be completely different due to empiric administration of blood products and medication. It should not come as a surprise since traditional coagulation testing was not designed for quick coagulation diagnosis in the surgical period. The purpose of conventional testing is to predict isolated coagulation defects such as hemophilia (aPTT) or to monitor treatment with oral anticoagulants (PT and INR). Prothrombin time and aPTT are based on non-physiological situations, testing ex vivo fibrin formation after artificial stimulation. Citrated blood is centrifuged; plasma is re-calcified and activated in a crystal tube in which several optical measurements detect the beginning of the coagulation process or fibrin formation. Traditional testing cannot determine the velocity of thrombi formation, strength, and tendency to dissolution. The effect of platelet, VWF, FXIII inhibitors, and cellular components do not affect standard testing. The recent hemostasis model highlights the importance of platelet activation and amplification in its surface in live coagulation models (Hoffman and

Factor	PT	aPTT	*In vivo*
Fibrinogen (mg / dL)	100	60	50-100
Prothrombin (%)	50	15	20–30
Factor V (%)	50	40	20
Factor VII (%)	50	NA	10
Factor X (%)	60	25%	20
Factor VIII (%)	NA	35%	40
Factor IX (%)	NA	20%	30
Factor XI (%)	NA	30%	50
Factor XII (%)	NA	20%	0
Factor XIII (%)	NA	NA	5
vWF (%)	NA	NA	30

Fig. 1 The coagulation factors plasma level necessary to keep normal hemostasis in vivo. *PT* prothrombin time, *aPTT* activated partial thromboplastin time, *NA* not affected, *vWF* Von Willebrand factor. (Modified from Tanaka et al. 2009)

Monroe 2001). Due to this fact, the role of traditional testing is limited in the live coagulation process.

Figure 1 shows the coagulation factors plasma level necessary to keep normal hemostasis in vivo. The relationship between coagulation time and coagulating factors is not linear; it is exponential (Dzik 2004). Due to this fact, abnormal coagulation testing is not necessarily associated with the critical plasma level of coagulation factors. Plasma levels of 20–30% of coagulating factors are necessary to achieve normal hemostasis, but it will require 40–50% plasma levels for traditional coagulation testing to be routine. Blood loss equivalent to 50% of the blood volume replaced by crystalloids (dilution) is associated with abnormal coagulation testing but is not always associated higher propensity to bleeding. PT and aPTT are more affected by a moderated decrease (up to 75%) of several factors than the decrease of an isolated factor below 50% of its level.

In the perioperative period, there is rarely an isolated decrease of a single factor; instead, there is usually a generalized decrease of all factors, including fibrinogen. Fibrinogen level is severalfold above the critical value of 100 mg/dL, below that is associated with a bleeding tendency. This critical value is reached when there is a blood loss of 1.4 of the blood volume. When blood loss is about two blood volumes, required levels of platelets and other coagulating factors are reached, and the tendency to further bleeding is enhanced (Hiippala et al. 1995). Most guidelines recommend fibrinogen levels higher (150–200 mg/dL) than the critical value described by the Hiippala et al. study in 1995. This is because critical levels are achieved sooner with less hemodilution (Kozek-Langenecker et al. 2013; Spahn et al. 2013). It is difficult to picture that a complex process like coagulation, which requires changes in the physical properties of the blood from a liquid to solid (clotting) and from solid to fluid (fibrinolysis), can be characterized with only two coagulation tests, platelet count, fibrinogen level, and D-dimer. These traditional tests do not evaluate the whole hemostatic process but only just some punctual aspects of it.

Two questions come up when we face a hemorrhagic patient in the clinical setting, either in the operating room or the intensive care unit. First, what is the cause of the bleeding? Second, can we fix it? Oftentimes this question is addressed based only on traditional coagulation testing, and the treatment is primarily empiric with overuse of blood products, which is not free of risks (Karam et al. 2015). Many times, the lonely clinician is unable to answer these two questions with the right tools to achieve a goal-directed therapy with medication and blood products.

Table 3 summarizes the limitations of conventional coagulation laboratory testing (Weber et al. 2013).

Point of Care Monitoring

Thromboelastography (TEG®) and Thromboelastometry (ROTEM®)

The TEG/ROTEM attempt to address the initial two questions (What is the cause of the bleeding? How can we fix it?) by detecting the changes in the physical properties of the blood that reflect the hemostasis by the interaction of the whole blood components (Fig. 2).

Table 3 Limitations of conventional laboratory coagulation analyses

Test performed at a standardized temperature (37 °C), impeding the detection of coagulopathies induced by hypothermia
The global test (aPTT, INR/Quick) reflects only the initial formation of thrombin in plasma and is unaffected by any of the corpuscular elements of the blood
Conventional coagulation tests do not provide any information about clot stability over time or regarding fibrinolysis
The platelet count is quantitative and cannot detect pre-existing, drug-induced, or perioperatively acquired platelet dysfunction
Performing conventional laboratory analyses and reporting coagulation test results take 40–90 min after blood drawing

The coagulation process has four phases that correspond with the current coagulation process:

1. Primary hemostasis is the interaction between the vascular components, platelets, and vWF.
2. Second is the thrombin production triggered by the activation of factor X through the tissue factor (TF)-activated Factor VII (FVIIa) complex.
3. The third is the thrombi formation by fibrin polymerization and finally the clot stabilization by the factor XIII.
4. Clot lysis.

Traditional coagulation testing (PT and aPTT) reflects the beginning of thrombin generation (Fig. 2). Conventional coagulation testing cannot assess primary hemostasis, clot formation, and clot lysis.

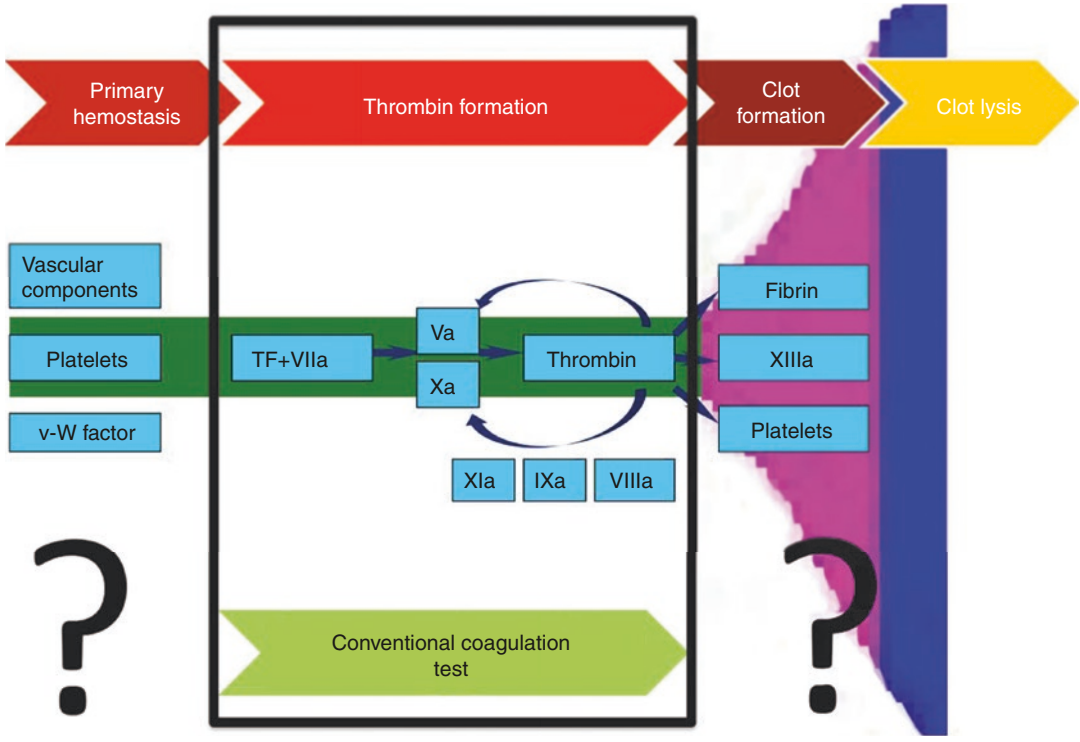

Fig. 2 Diagram of the coagulation process showing the areas that are unseen by conventional testing (question mark)

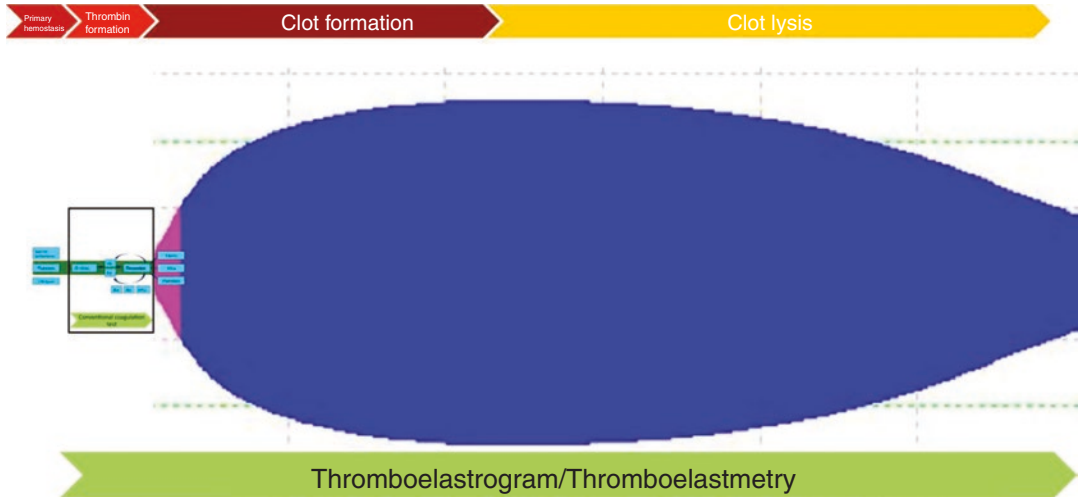

Fig. 3 Coagulation process (below). Conventional testing only reports the beginning of thrombin generation (black square). TEG®/ROTEM® report in addition to thrombin generation, the clot formation, and lysis

History and Nomenclature

The thromboelastography (TEG®) was described first by Helmut Hartert in 1948 in Heidelberg before introducing aPTT in clinical practice. It was fairly popular in the '80s as a proper technique to assess the hemostatic process, particularly at the beginning of liver transplant programs. In Fig. 3, the different stages of coagulation can be compared between traditional testing (Green arrow inside de black square) and TEG/ROTEM which in addition to assess the thrombin formation, also shows the development of the clot and its strength linked to platelets function, fibrin, Factor XIII. Finally, TEG/ROTEM shows the lysis of the clot (long arrow).

Even though TEG was helpful since the beginning, it was troublesome for clinical use due to the management complexity and extreme sensitivity to vibration. In 1993 Haemoscope Corporation, IL, USA patented the term TEG and currently, Haemoscope is a division of Haemonetics Corporation (Fig. 4).

Latterly Pentapharm GMBH, Munich patented a new device based on similar principles and used the term ROTEM (Rotation thromboelastometry) (Fig. 5). Both tests are similar; some have the TEG ending (Thromboelastography, Thromboelastogram) and others the TEM ending (Thromboelastometry, Themogram). Currently, the technology has improved. Management is easier and less sensitive to vibration, so it can be used in the surgical suite.

Operation Principles

Both devices had similar operation principles based on measuring the changes of the viscoelastic properties of the clot associated with fibrin polymerization. First, the blood sample is placed in the tray with other reagents. In the TEG the hanging pin is still, detecting the movement of the tray that rotates from right to left 4.75° on the longitudinal axis. In the ROTEM the tray is immobile, and the hanging pin spins. Once the coagulation process starts with fibrin production, there is a restriction of the pin on the tray that is integrated electronically and represented in a graph, which has a higher amplitude when there is higher resistance to movement (Fig. 6).

Graph Analysis and Parameters

Below we describe the different parameters needed to interpret ROTEM (Fig. 7) and TEG test (Fig. 8).

The time it takes since the measurement starts to the beginning of clot formation is called **R (reaction time) in TEG** and **CT (clotting time) in ROTEM.** It is the line from the start of the

Fig. 4 Photograph of the TEG® 5000 hemostasis analyzer and related software screenshot, used by permission of Haemonetics Corporation

Fig. 5 Photograph of the ROTEM delta hemostasis analyzer. (Courtesy of Werfen, Barcelona, Spain)

graph until it reaches 2 mm in amplitude. It is measured in seconds, and it shows the speed of fibrin formation. It is affected by plasma coagulation factors and circulating anticoagulants.

The time it takes between the amplitude of the graph to increase from 2 to 20 mm wide is called **K (clot kinetics), α angle in TEG and CFT (clot formation time) in ROTEM.** It is measured in seconds and conveys the kinetics of clot formation. It is a non-specific parameter since it is influenced by coagulating factors, anticoagulants, fibrin polymerization, and clot stability (platelets, fibrin, and FXIII).

Maximal graph amplitude (MA in TEG) or maximum clot firmness (MCF in ROTEM). It is measured in mm and is one of the essential parameters since it reports the maximal clot firmness through increased fibrin polymerization, platelets, and FXIII. FIBTEM or functional fibrinogen can differentiate between the platelets or fibrinogen contribution to the clot firmness.

ML (maximum lysis in ROTEM) is the reduction of clot firmness after MCF in relationship with time. It is presented in a % of the MCF. If the clot is stable, the ML is <15%. Fibrinolysis is considered when the ML is >15%. In the **TEG**, the **LY30 and LY60** measure the percentage of lysis at 30 and 60 min. LY30 is considered abnormal when >7.5%.

In TEG, a hemostatic index **(CI, coagulation index)** integrates R, K, α, and MA. Normal range for CI is −3 to +3, values <−3 represent hypocoagulable and >3 is hypercoagulable states.

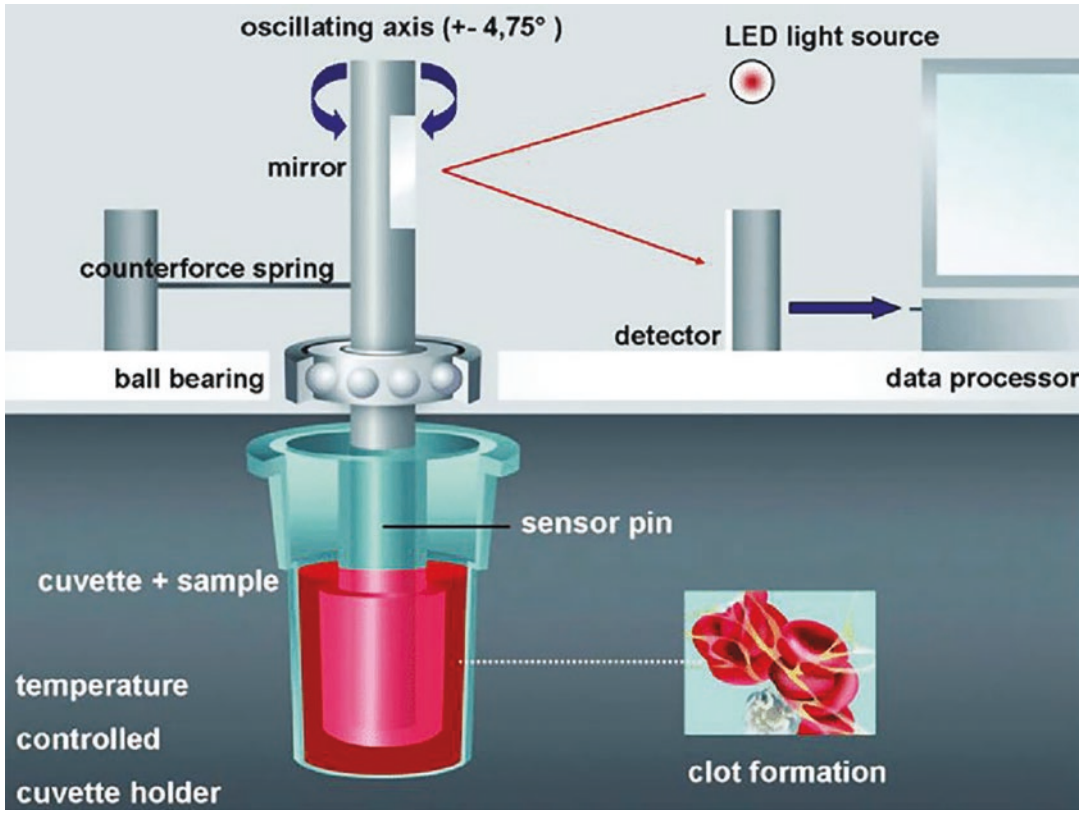

Fig. 6 Illustration of the ROTEM detection principle. (Courtesy of Werfen, Barcelona, Spain). A whole blood sample is placed into a cuvette, and a cylindrical pin is immersed. Between pin and cuvette remains a gap of 1 mm, bridged by the blood. The pin is rotated by a spring to the right and the left. If the blood is liquid, the movement is unrestricted. However, when blood starts clotting, the clot increasingly restricts the rotation of the pin with rising clot firmness. In TEG, this kinetic is detected mechanically and calculated by an integrated computer to the typical curves and numerical parameters. In TEG the principle is similar, but the tray spins while the pin is fixed

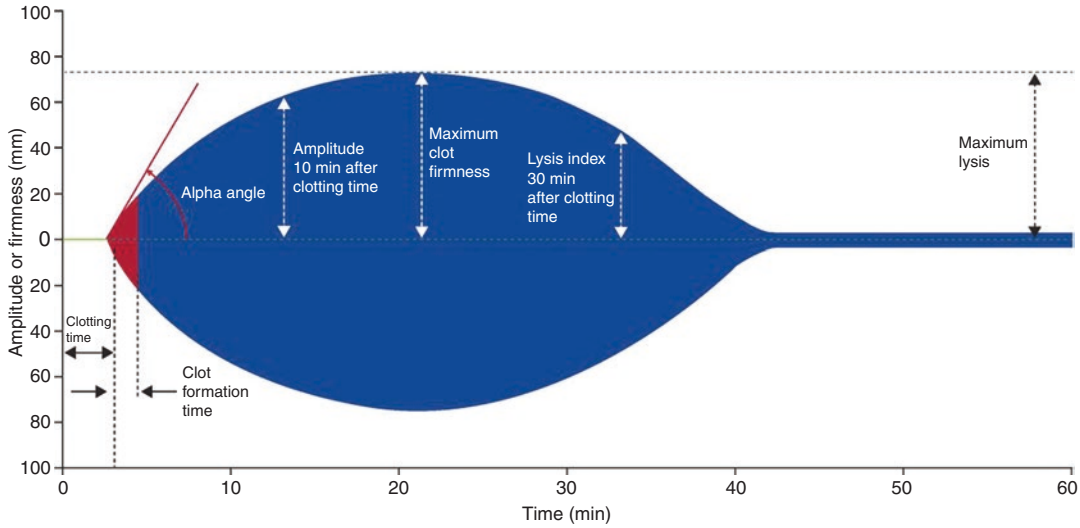

Fig. 7 ROTEM graph and parameters (TEMogram). (Courtesy of Werfen, Barcelona, Spain)

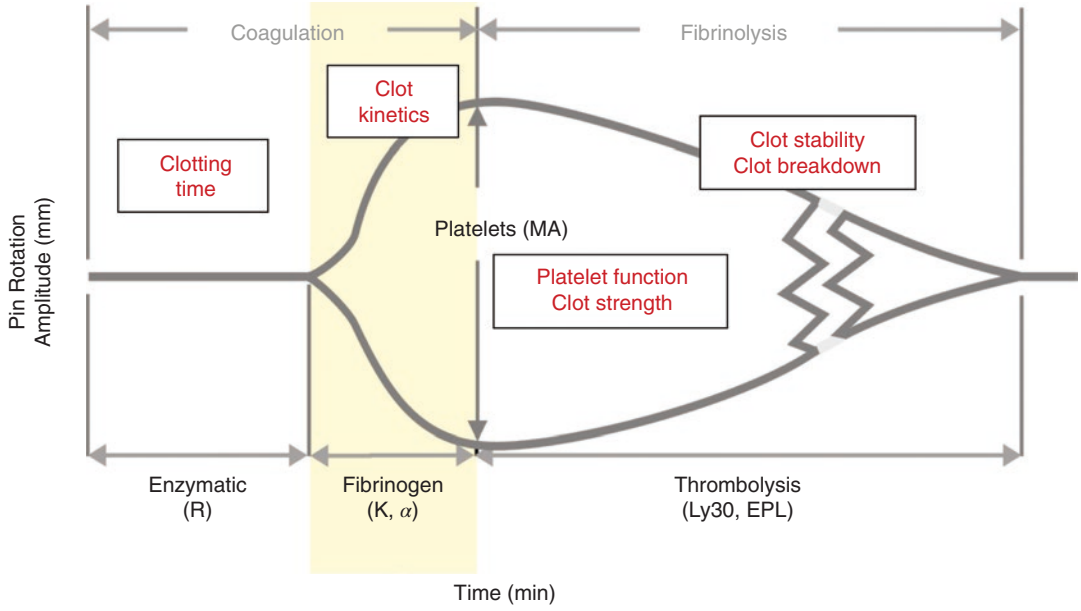

Fig. 8 TEG hemostasis analyzer graph and parameters. (Image used by permission of Haemonetics Corporation)

Table 4 TEG hemostasis analyzer table of normal values, used by permission of Haemonetics Corporation

	R (min)	α (degree)	*K* (min)	MA (mm)	LY30 (%)	CI (coagulation index)
Kaolín	4–8	47–74	0–4	54–72	>7.5% fibrinolysis	< −3 hypocoagulability > +3 hypercoagulability
R-TEG	0–1	66–82	1–2	54–72	>7.5% fibrinolysis	
FF	n.d.	n.d.	n.d.	9–29	n.d.	n.d.

R-TEG Rapid TEG, *FF* functional fibrinogen, *min* minutes, *mm* millimeters, *n.d.* no data

Table 4 shows typical values for TEG and Table 5 for ROTEM sigma.

Types of Testing

Thromboelastometry (ROTEM®)

- The test is performed in citrated blood, which implies the citrate reversal by adding calcium chloride to the blood sample. The ROTEM delta pipetting is automatic, which facilitates the process. The new ROTEM sigma needs a sample of whole citrated blood that is processed by a cartridge that allows fully automated test operation, avoiding pipetting and sample manipulation. The samples need to be run ideally within 2 h of the sample extraction to a maximum time of 4 h.
- **EXTEM** is an in vitro semi-quantitative testing on citrated blood re-calcified through the extrinsic pathway activation by the thromboplastin (tissue factor). It measures the coagulation pathway to the clot formation and subsequent fibrinolysis (Factors involved VII, X, V, II, I, platelets). Liquid reagents for the ROTEM delta system EXTEM and the "beads" reagents used in the ROTEM sigma cartridge contain heparin inhibitors what enables the use and interpretation of these assays even under high heparin concentrations, such on cardiopulmonary bypass. However, single-use reagents are also available for ROTEM delta and ROTEM platelet. They must not be used in patients treated with unfractionated heparin because they do not contain a heparin inhibitor (Görlinger et al. 2019).
- **INTEM** is an in vitro semi-quantitative testing on citrated blood re-calcified through the activation of the intrinsic pathway by the

Table 5 Preliminary reference ranges for ROTEM *sigma* from Tem Innovations GmbH, Munich, Germany, 2015

Test name (reagent)	CT (s)	CFT (s)	α Angle	A5 (mm)	A10 (mm)	A20 (mm)	A30 (mm)	MCF (mm)	LI 30 (%)	LI 45 (%)	LI 60 (%)
INTEM C	161–204	62–130	66–77	33–52	43–62	50–68	51–69	51–69	98–100	92–100	87–100
HEPTEM C	160–211	58–127	67–78	34–53	45–63	52–68	53–69	53–69	98–100	93–100	88–100
	Comparison with INTEM C. A better clot formation in HEPTEM C as compared to INTEM C indicates the presence of heparin or heparin-like anticoagulants in the sample										
EXTEM C	50–80	46–149	63–83	32–52	43–63	52–70	54–72	55–72	100–100	98–100	94–100
APTEM C	41–80	62–184	60–80	28–50	39–61	48–68	51–71	52–71	100–100	98–100	93–100
	Comparison with EXTEM C. A better clot formation in APTEM C as compared to EXTEM C is a sign of hyperfibrinolysis. LI in APTEM C represents platelet-mediated clot retraction of factor XIII deficiency										
FIBTEM C	46–84	n.d.	n.d.	5–20	6–21	6–21	6–21	6–21	91–100	89–100	89–100
	Only the amplitude values are used in the FIBTEM C test for clinical interpretation of the fibrinogen contribution *Low amplitude in FIBTEM C indicates the presence of a fibrinogen deficiency or fibrin polymerization disorders*										

s seconds, *mm* millimeters, *n.d.* no data

ellagic acid. It measures the coagulation pathway to the clot formation and subsequent fibrinolysis (Factors involved XII, XI, IX, VII, X, V, II, I, and platelets).

– **FIBTEM**: Precisely monitors fibrinogen function. The activation of coagulation is like EXTEM, but the reactants contain cytochalasin D that inactivates the platelets. The clot formed depends only on polymerization and fibrin formation. If we compare it with EXTEM, we can estimate the contribution of the platelets to the maximal clot firmness.
– **APTEM** activates the coagulation like EXTEM, but the reactants contain aprotinin which causes an in vitro inactivation of the fibrinolysis. The comparison between EXTEM with APTEM results infers if there is fibrinolysis if the APTEM results are better.
– **HEPTEM**: similar coagulation activation like INTEM, but the reactant has heparinase. Comparing the INTEM with HEPTEM, we can detect if the coagulation anomalies are related to heparin and can be corrected with protamine.
– **NATEM** is global in vitro semi-quantitative testing on citrated blood re-calcified without a coagulation activator. The coagulation gets activated through the contact between the pin and the tray. Similar testing can be done in the TEG. However, testing without coagulation activators is of little clinical use since there is a long latency before the results and has no advantages with traditional coagulation testing.

The ROTEM has four channels, and it can run four simultaneous tests that need to be chosen depending on the clinical setting. Usually, we run EXTEM, INTEM, and FIBTEM, saving the last channel for the HEPTEM in patients who have been heparinized or there is a suspected alteration of the intrinsic pathway (e.g., heparinized patient or unclamping of liver transplant). APTEM is used in patients that we suspect fibrinolysis.

Different algorithms have been published, but the most popular and reliable are the evidence-based algorithms posted by Dr. Gorlinger (Görlinger et al. 2019). The aims of these algorithms include administering the **proper hemostatic intervention(s)**, in the **correct dose** (fibrinogen and platelet dose calculation, Table 2), at the right time **("Treat fist what kills first!"),** and in the proper sequence, as shown in algorithms in Figs. 9 and 10. It is important to note that the first decision in these ROTEM-guided bleeding management algorithms is the clinical question of whether diffuse (coagulopathic/microvascular) bleeding is present. If the answer is "No," the ROTEM algorithm ends at this point. ROTEM results should be interpreted in a proper sequence ($A5_{FIB}$ before CT_{EX}) as given by the algorithms, not according to their availability (CT_{EX} before $A5_{FIB}$). This avoids potential misinterpretation of ROTEM results.

Figures 9 and 10 show evidence-based algorithms for ROTEM (A5)-guided bleeding management in adult and pediatric cardiovascular surgery.

Thromboelastography (TEG®)

The TEG can run on citrated blood if the sample cannot be processed immediately or run after blood is drawn (within 4 min from extraction). If citrated blood is used, it must be reversed with 20 μL calcium chloride 0.2 M to the tray. In TEG 5000 pipetting is manual, and the testing is as follows:

- **Kaolin** is a global test activated by kaolin. It measures coagulation activation, clot consolidation, and later fibrinolysis (Fig. 11).
- **Heparinase**: it measures the heparin effect compared with regular kaolin testing. The test is like the kaolin test but uses a blue tray with heparinase.
- **Functional fibrinogen assay** adds to the blood sample tissue factor and platelet inhibitor to separate the fibrinogen and platelet's function. It estimates the fibrinogen function.
- **Rapid TEG** speeds the coagulation process by triggering the intrinsic and extrinsic coagulation pathways by adding to the sample tissue factor, kaolin, and phospholipids. The results turnover is quicker and monitors heparin anticoagulation by a specific (TEG ACT). It is used for rapid coagulation evaluation in the multiple trauma setting.
- **Platelet Mapping** allows anti-platelets agents monitoring. It activates platelets by adding ADP, arachidonic acid, or both. It is beneficial to detect the risk of bleeding in the anti-aggregated surgical patient.

The equivalence between TEG and ROTEM is shown in Fig. 12. Even though there is a similarity between TEG and ROTEM measurements, they are not entirely interchangeable (Venema et al. 2010; Solomon et al. 2012).

Results Interpretation

It may be intimidating for the neophyte with this technology, but the interpretation of the results is easy and intuitive. An experimented physician only seeing the graph without the values can estimate the patient's hemostasis. Figure 13 shows a graph display of ROTEM that helps to understand coagulation evaluation easily.

In summary, to facilitate understanding, TEG and ROTEM testing, assess individually coagulation factors (green line), platelet function, and fibrinogen. The last two are measured together in global testing in both systems, but fibrinogen can be assessed individually along with fibrinolysis (FIBTEM or functional fibrinogen). On the left side of Fig. 13, global tests such as EXTEM or INTEM (navy blue graph) and the isolated fibrinogen function test (pink graph). There is no isolated platelet function testing, but if you subtract the fibrinogen testing to the global testing graph, you can estimate the platelet function (right side graph). Fibrinolysis can be observed by the graph tapering in the form of a teardrop.

Of course, the initial impression of reviewing the graph display should be verified with the numeric data in clinical practice.

Lately, TEG and ROTEM testing have improved their technology to become user-friendly and less sensitive to vibration. ROTEM has added to the ROTEM *delta* system a platelet module (the ROTEM *platelet*) working by impedance aggregometry and measuring platelet function in whole blood. In addition, both TEG and ROTEM have launched new fully automated systems; **TEG 6 s** (resonance method) and **ROTEM sigma** systems that have avoided the need for manual, controlled pipetting, or prior manipulation of reagents. The only requirement is to transfer a small amount of blood to the loaded cartridge and wait for the trace (Fig. 14).

Other devices to carry out viscoelastic tests have been developed in recent years, such as the Quantra QPlus System (Sonorheometry) and the ClotPro system (Elastic Motion Thromboelastography), with a still small number of publications and limited evidence.

Indications and Limitations of Thromboelastography and Thromboelastometry

Since the beginning, thromboelastography has been used in the operating room and ICU, especially in cardiac surgery and liver transplantation.

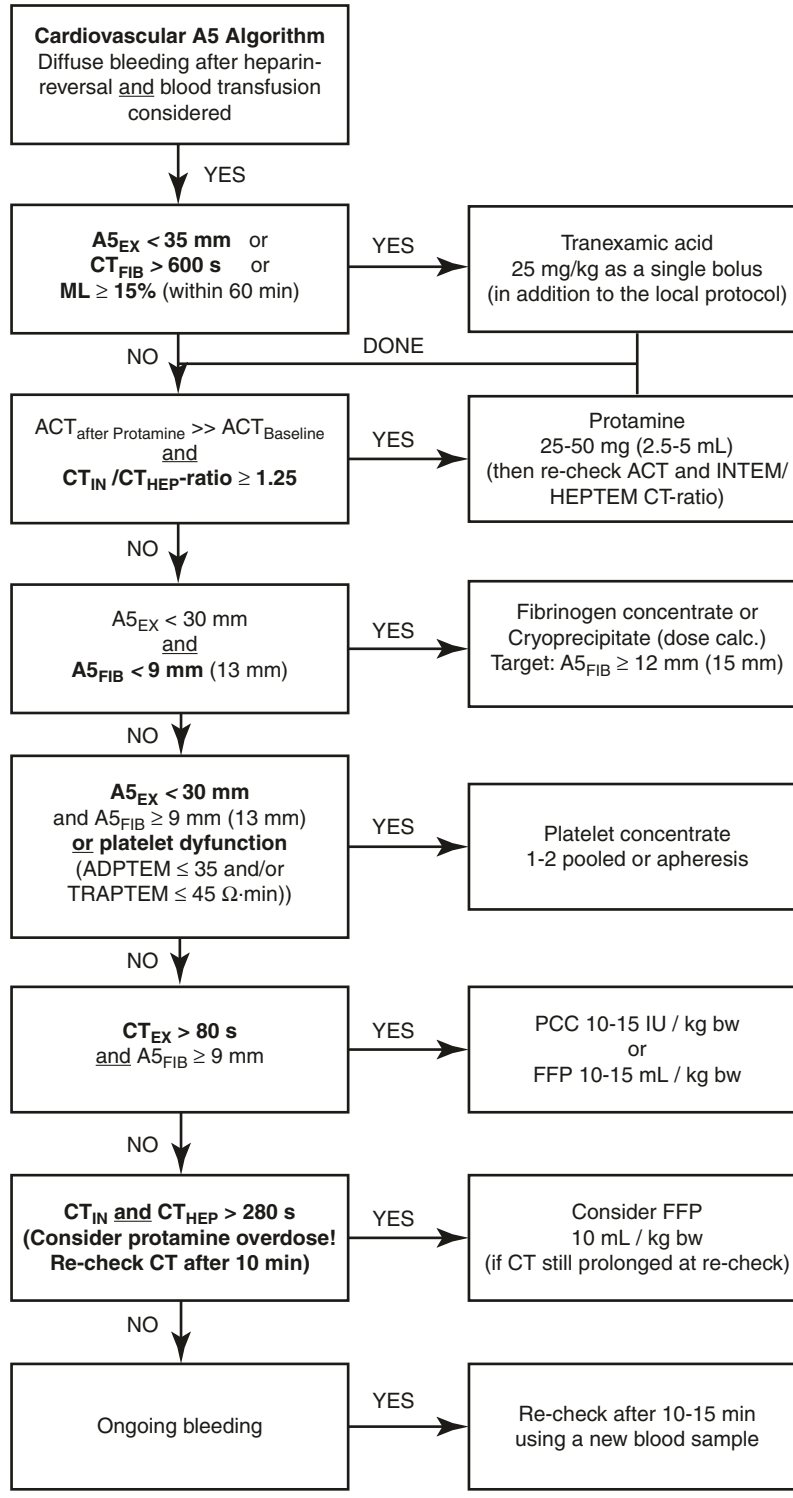

Fig. 9 Evidence-based algorithm for ROTEM (A5)-guided bleeding management in adult cardiovascular surgery. (Courtesy of Dr. Klaus Görlinger, Munich, Germany). $A5_{EX}$ amplitude of clot firmness 5 min after CT in EXTEM, *mm* millimeters, CT_{FIB} coagulation time in FIBTEM (CT_{FIB} > 600 s reflects a flat-line in FIBTEM), *s* seconds, *ML* maximum lysis (within 1 h run time), *min* minutes, *ACT* activated clotting time, CT_{IN} coagulation time in INTEM, CT_{HEP} coagulation time in HEPTEM, *mL* milliliters, $A5_{FIB}$ amplitude of clot firmness 5 min after CT in FIBTEM, *ADPTEM* ROTEM platelet test in which platelet aggregation is induced by adenosine diphosphate, *TRAPTEM* ROTEM platelet test in which platelet aggregation is induced by arachidonic acid, CT_{EX} coagulation time in EXTEM, *bw* body weight, *PCC* four factor prothrombin complex concentrate, *FFP* fresh frozen plasma

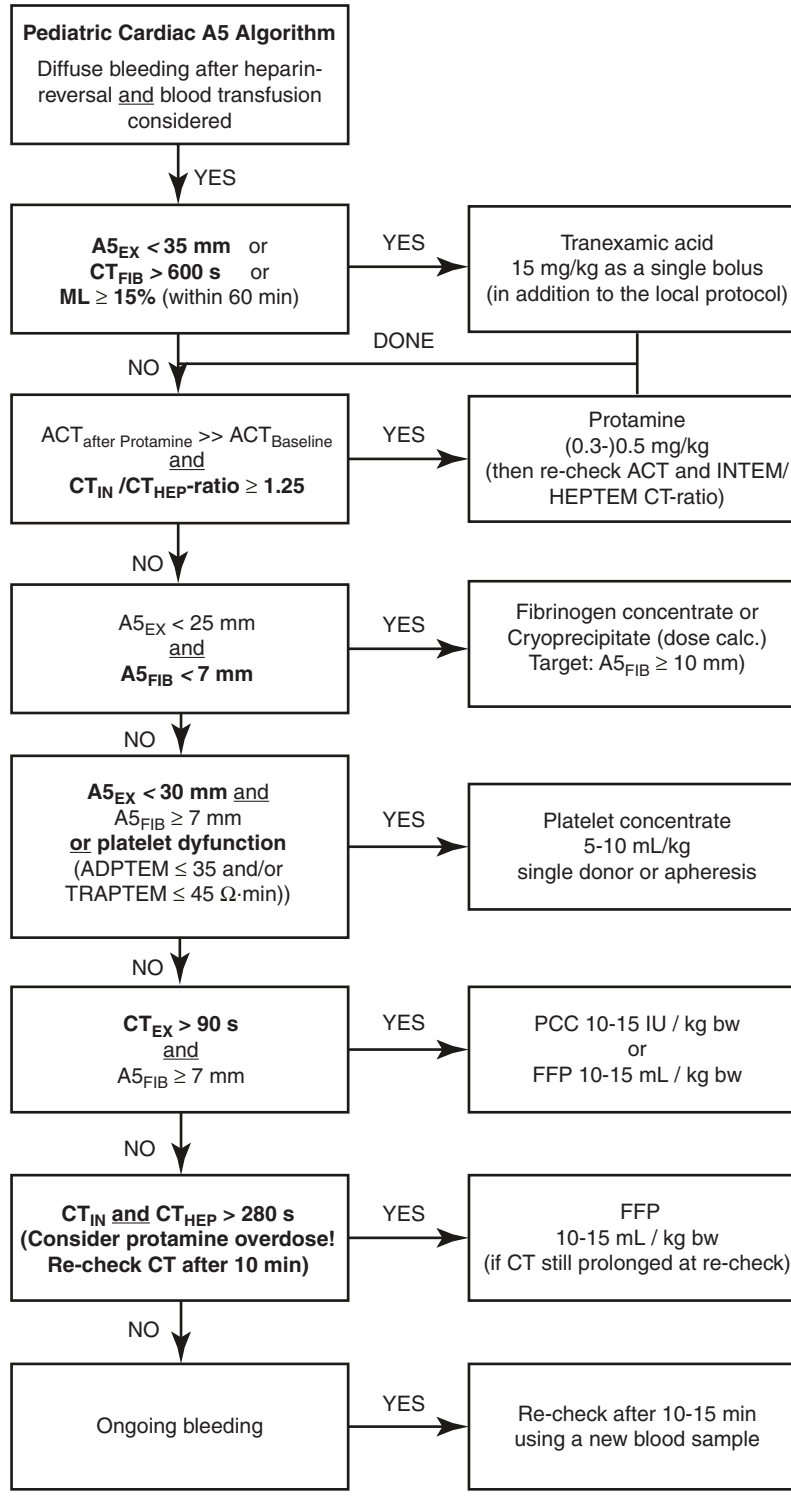

Fig. 10 Evidence-based algorithm for ROTEM (A5)-guided bleeding management in pediatric cardiovascular surgery. (Courtesy of Dr. Klaus Görlinger, Munich, Germany). $A5_{EX}$ amplitude of clot firmness 5 min after CT in EXTEM, *mm* millimeters, CT_{FIB} coagulation time in FIBTEM (CT_{FIB} > 600 s reflects a flat-line in FIBTEM), *s* seconds, *ML* maximum lysis (within 1 h run time), *min* minutes, *ACT* activated clotting time, CT_{IN} coagulation time in INTEM, CT_{HEP} coagulation time in HEPTEM, *mL* milliliters, $A5_{FIB}$ amplitude of clot firmness 5 min after CT in FIBTEM, *ADPTEM* ROTEM platelet test in which platelet aggregation is induced by adenosine diphosphate, *TRAPTEM* ROTEM platelet test in which platelet aggregation is induced by arachidonic acid, CT_{EX} coagulation time in EXTEM, *bw* body weight, *PCC* four factor prothrombin complex concentrate, *FFP* fresh frozen plasma

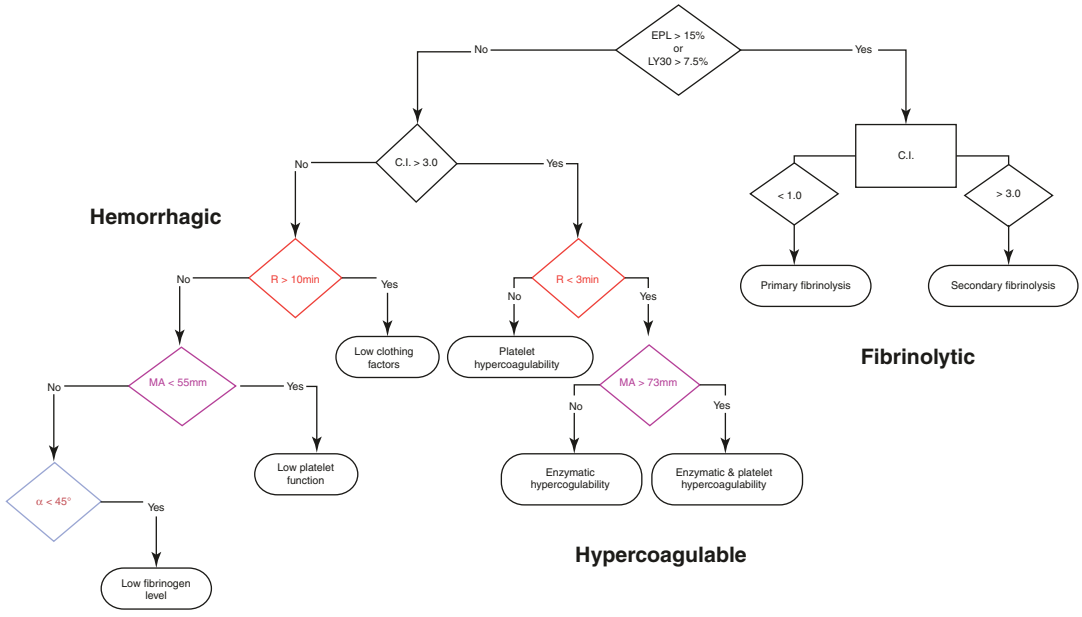

Fig. 11 TEG interpretation algorithm used by permission of Haemonetics Corporation

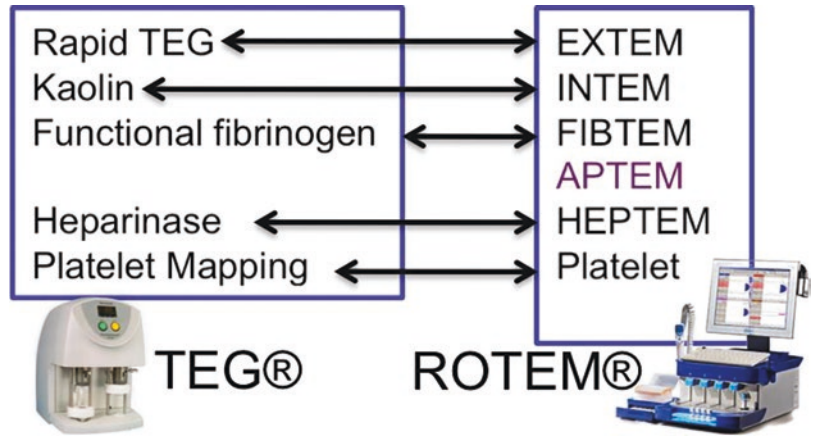

Fig. 12 Approximate equivalence between TEG and ROTEM testing

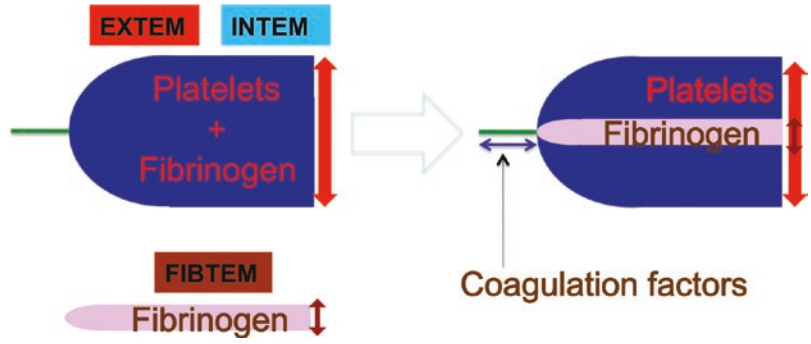

Fig. 13 ROTEM graph interpretation

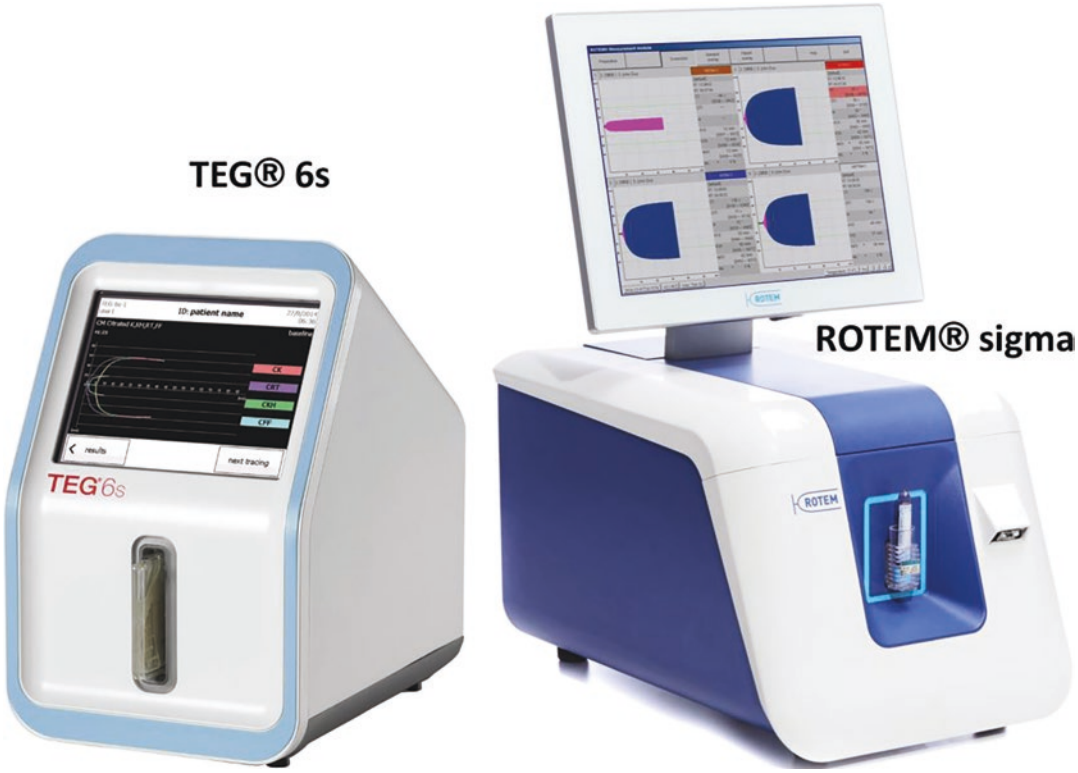

Fig. 14 Photographs of the latest devices developed by TEG and ROTEM. (They are published with the permission of Haemonetics Corporation and Werfen, Barcelona, Spain)

Currently, its use has been expanded to any bleeding situation where coagulopathy is involved, and prompt diagnosis and guided treatment are beneficial (Table 6). However, the clinical evidence for its use is still limited (Haas et al. 2014).

Even though these tests are performed in whole blood and currently is the best test available, it must be kept in mind that it is still an "in vitro" test that does not account for fluid dynamics in the vessels and endothelial interaction. For example, these are not useful for Von Willebrand disease. In addition, the coagulation activators added induced coagulation without the participation of primary hemostasis. The primary hemostasis and platelet function cannot be evaluated by visco-elastic testing, and it is released in the ROTEM fact sheet. The effect of aspirin and ADP antagonist (e.g., clopidogrel or ticlopidine) can only be evaluated by specific testing. When there is a severe alteration of platelet function through glycoprotein IIb/IIIa inhibition, either pharmacological or congenital (Glanzmann thrombasthenia), it could affect the maximal amplitude

Table 6 Common and recent indications of viscoelastic testing

• Major surgery
– Cardiac surgery
– Liver transplant
– Scolisis
– Vascular surgery
• Major bleeding:
– Multiple trauma
– Obstetric hemorrhage
• Severe burn
• Heparinized patients: ECMO and VAD (ventricular assist device)
• Acute normovolemic hemodilution
• Medical disorders: hemopoyetic, liver and renal disease
• SARS-CoV-2 coagulopathy

Table 7 Indications and limitations of viscoelastic testing

Indications of thromboelastography and thromboelastometry use:
• Bedside testing with short turnover
• Global test of coagulation in whole blood
• An easy model of interpretation of coagulation
• Guided treatment (blood products and medications)
• Cardiac surgery and liver transplant
• Massive hemorrhage: Multiple trauma and obstetric hemorrhage
• Procoagulant state diagnosis and anti-procoagulant treatment diagnosis
Thromboelastography limitation
• Static "in vitro" testing
• Does not assess primary hemostasis (Von Willebrand disease)
• Difficulties in standardizing the sample processing
• Different equipment with different activators
• Limited sensitivity to antiaggregant treatment
• Requires individual training to run (old models) and interpret testing
• Needs quality control by personnel outside the laboratory

of the trace and the clot firmness. Another limitation is the low sensitivity to oral anticoagulants (e.g., coumadin) or low molecular weight heparin administration. For these drugs, there is specific testing, including INR and anti-Xa activity, respectively. The indications and limitations of visco-elastic testing are summarized in Table 7.

Platelet Function Testing

Numerical and functional platelet disorders are common among pediatric cardiac surgery patients. Therefore, a platelet function test can be helpful to screen high-risk patients.

PFA-100

The PFA-100 (Siemens Healthcare, Malvern, PA, USA) analyzes platelet function in which citrated whole blood is aspirated at high shear rates through disposable cartridges containing an aperture within a membrane coated with either collagen and epinephrine (CEPI) or collagen and ADP (CADP). These agonists induce platelet adhesion, activation, and aggregation leading to rapid occlusion of the aperture and cessation of blood flow termed the closure time (CT). The PFA-100 can help screen patients with von Willebrand disease or a platelet GP Ib defect (Bernard-Soulier syndrome) and is often used to establish the presence or absence of aspirin resistance. The PFA-100 has a high negative predictive value (98%) to identify patients not needing platelet transfusions after cardiac bypass (Slaughter et al. 2001). Suppose the PFA-100 gives a normal result (78–199 s for the CEPI cartridge, 55–137 s for the CADP cartridge). In that case, primary hemostasis is intact and so may prevent the further screening of platelet function. There are some exceptions such as storage pool deficiency, primary secretion defects, mild Type 1 vWD. However, its use in the bleeding patient is not well characterized as the tests may not work well in dilutional coagulopathy (Theusinger et al. 2015).

VerifyNow System

(Accumetrics, Inc., San Diego, CA) and **Whole-blood Impedance Aggregometry** (Multiplate, DynaBite, Munich, Germany) are used increasingly to monitor therapeutic responses to aspirin, P_2Y_{12} antagonists (ticlopidine, clopidogrel, prasugrel, ticagrelor, etc.), and GP IIb/IIIa inhibitors (abciximab or eptifibatide).

The VerifyNow System is a whole blood point-of-care test that measures platelet-induced aggregation as an increase in light transmittance. It detects platelet activity by measuring in vitro platelet aggregation in a blood sample exposed to specific agonists. This includes inhibition of platelet activity in response to antiplatelet therapies. There are three types of VerifyNow tests: Aspirin, PRUTest (P2Y12), and IIb/IIIa. Each test device contains a lyophilized preparation of human fibrinogen-coated beads and a platelet agonist. The platelet agonist varies by test type. Each test is based upon the ability of GP IIb/IIIa receptors on activated platelets to bind to fibrinogen-coated beads. When the activated platelets are exposed to the fibrinogen-coated beads, aggregation occurs in proportion to the number of available platelet receptors. The instrument is designed to measure this aggregation as an increase in light transmittance, allowing detection and quantification of antiplatelet medication effect.

Table 8 Test available for Multiplate analyzer

Test	Activation	Sensitivity	Not sensitive for
ASPI test	Arachidonic acid: Is converted to TXA2 by platelet-own cyclooxygenase	Aspirin, Gp IIb/IIIa antagonists	Clopidogrel, vWF
ADP test	ADP: Binds onto platelet ADP receptors	Clopidogrel, Gp IIb/IIIa antagonists	Aspirin, vWF
ADP test HS	ADP + prostaglandin E1 (prostaglandin is a natural inhibitor and enhances the sensitivity of the assay for clopidogrel)	Clopidogrel, Gp IIb/IIIa antagonists	Aspirin, vWF
TRAP test	TRAP-6 (thrombin receptor activating peptide): TRAP-6 is a potent agonist which mimics the platelet-activating action of thrombin	Gp IIb/IIIa antagonists	vWF, aspirin, clopidogrel (weak effect on TRAP test)
COL test	Collagen: Collagen activates platelet and triggers a release of arachidonic acid from the platelet membrane, which is converted to TXA2 by the cyclooxygenase	Aspirin, Gp IIb/IIIa antagonists	Clopidogrel, vWF
RISTO test	Ristocetin: vWF dependent platelet activation via the Gp Ib receptor	Bernard-Soulier syndrome, severe vWD, aspirin	Mild vWD

TXA2 thromboxane A2, *Gp* glycoprotein, *vWF* von Willebrand Factor, *ADP* adenosine diphosphate

The Multiplate analyzer

is a POC impedance aggregometer to detect and quantify the effect of antiplatelet medication. The device consists of 5 channels for contemporary tests, an integrated computer, and guided automatic pipetting. The Multiplate device's measurement principle is electrical impedance—the electrical current passes through individual sets of electrodes. Whole blood sample platelets bind to and cover the electrodes in a small monolayer when the electrodes meet. As the platelets become activated after exposure to a specific platelet agonist, the platelets firmly adhere to the electrodes and begin to aggregate. An increase in the number of platelets adhering to the electrodes increases the resistance (impedance) between the electrodes. The Multiplate records platelet aggregation at approximately 0.5 s intervals, and its software plots these changes as a curve. Three parameters are calculated: aggregation, the area under the aggregation curve (AUC), and velocity. The most critical parameter is the AUC. AUC is recorded as Units or U. It is affected by the total height of the aggregation curve and its slope and is best suited to express the overall platelet activity. The aggregation (in AU) is the maximum height of the curve during the measurement period, and the velocity (in AU/min) is the maximum slope of the curve (Table 8).

TEG Platelet Mapping

The whole blood Thrombelastograph (TEG) Platelet Mapping assay (Haemoscope Corporation, Niles, Illinois, USA) measures clot strength, maximal amplitude (MA), reflecting maximal platelet function, and detects the reduction in platelet function, presented as percentage inhibition, by both aspirin (Tantry et al. 2005) and clopidogrel. The TEG Platelet Mapping assay relies on evaluating clot strength to enable a quantitative analysis of platelet function. Platelet Mapping is a modification of TEG allowing a specific examination of platelet function relating to two different agonists, arachidonic acid (AA), and adenosine-5-diphosphate (ADP). Platelets' thrombin activation (initiated in the TEG assay by contact with kaolin) is so robust that it masks any effect of secondary platelet activators. Therefore, this reaction is carried out in the setting of heparinized blood to block thrombin activation. Factor XIII is added to generate a baseline fibrin meshwork (generates fibrin) and represents minimal platelet activation. The contribution of the ADP or ThromboxaneA2 (TxA2)

Fig. 15 Photograph of the ROTEM delta plus platelet hemostasis analyzer. Courtesy of Werfen, Barcelona, Spain

receptors to the clot formation is provided by adding ADP or AA. The curves generated are compared to standard TEG trace. Platelet Mapping has shown a statistically significant correlation to optical platelet aggregation as the gold standard assay (Craft et al. 2004).

Platelet Mapping is helpful for the evaluation of adequate platelet inhibition by aspirin or clopidogrel (Craft et al. 2004), and it is helpful in percutaneous coronary angioplasty (PTCA). During these procedures, due to the endothelial damage and clot rupture in the coronary artery, the coagulation cascade is activated, and platelets have a vital role in the ischemic complications after PTCA. Platelet inhibition by GPIIb/IIIa receptor inhibitors is a potent therapy to reduce the risk of myocardial infarction and death. This test can monitor several types of drugs to secure adequate anti-aggregation, avoiding excessive inhibition that could derive from bleeding. TEG platelet mapping could predict excessive postoperative chest tube output and the need for platelet transfusion (Chowdhury et al. 2014).

The ROTEM *platelet*

ROTEM *delta* system incorporates a platelet module that works by impedance aggregometry, measuring platelet function in whole blood (Fig. 15).

With the influence of the Willebrand factor (vWF) at the place of the injury, the platelets stick to the exposed collagen (adhesion), leading to activation of other platelets. Fibrinogen plays a crucial role in the aggregation of platelets. The detection method works by placing a whole blood sample into a cuvette with two electrodes. After adding the reagent, the platelets are activated, aggregating to the electrodes within the next minutes. The measured impedance between the electrodes increases and is graphically displayed as a curve (Fig. 16). The result is represented via three parameters:

- **A6** (Ohm): **A6** shows the measured impedance at the measurement time of 6 min as the amount of platelet aggregation.
- **Maximum Slope** (Ohm/min): **MS** is the maximum slope of the aggregation graph and a measurement rate of aggregation.
- **The area under the curve** (Ohm*min): **AUC** contains the area under the aggregation curve from the start of measurement to 6 min and provides information on the overall platelet aggregation.

The reason for decreased platelet aggregation can be determined with the ROTEM *platelet,* differential diagnosis, and the tests ADPTEM, TRAPTEM, and ARATEM. Disturbed platelet aggregation is indicated by a decreased amplitude (curve). As causes, the intake of drugs that influence the platelet function or platelet dysfunctions due to extracorporeal assist devices, surgery, or others, must be considered. Drugs, which can affect platelet aggregation, are cyclooxygenase inhibitors (e.g., acetylsalicylic acid), GP IIb/IIIa receptor blockers (e.g., GP IIb/IIIa antagonists), or ADP receptor blockers (e.g., thienopyridines or direct ADP receptor antagonists). The results are available fast, and therefore a difference between surgical bleeding and platelet dysfunction can be made, and the monitoring of a platelet therapy is possible.

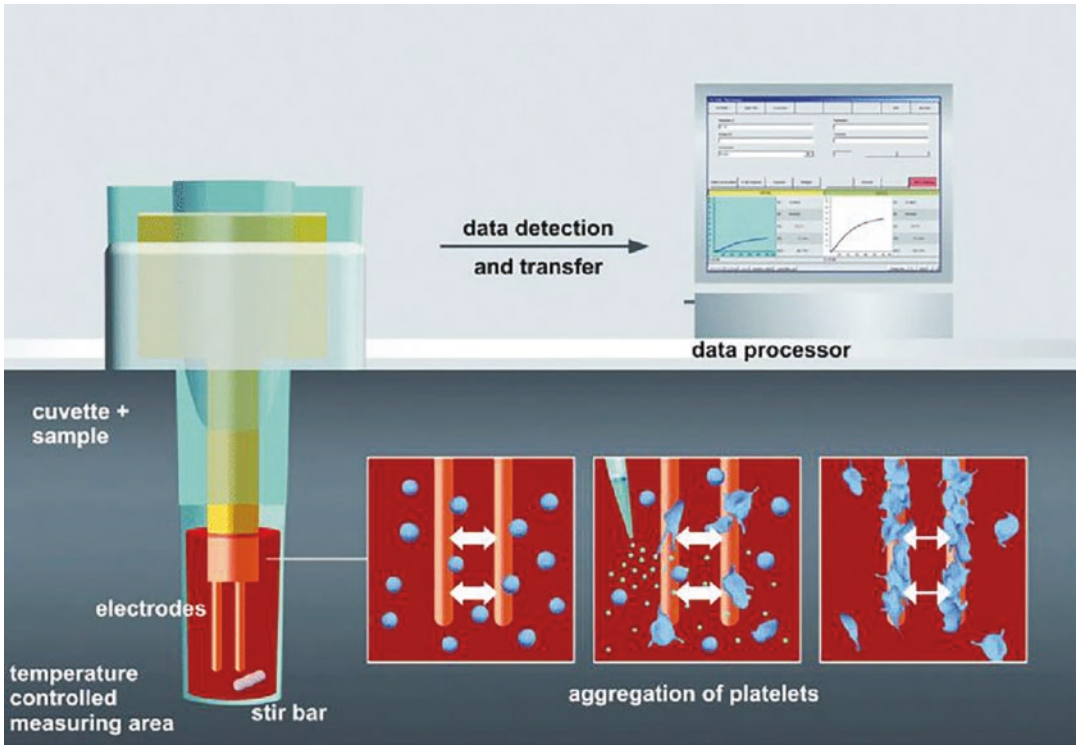

Fig. 16 Illustration of the ROTEM platelet measuring principle. Courtesy of Werfen, Barcelona, Spain. Activated platelets are aggregating on the surface of the test cuvettes' wires, thereby increasing the impedance between both wires. In addition, a magnetic stirrer prevents sedimentation of the blood cells during the 3 min incubation time

Monitoring Integration in Clinical Care

There is a limited predictive capability in cardiac surgery post-CPB with the available testing, but there is a high negative predictive value. In other words, if the TEG/ROTEM is normal, it rules out coagulopathy, and surgical causes of bleeding should be explored (Cammerer et al. 2003). The use of TEG helps to achieve prompt diagnosis and treatment of postoperative bleeding in cardiac surgery (Despotis et al. 2009). Once the patient is on CPB, there is a decrease in the maximal amplitude in all tests without platelet inhibitor (e.g., ROTEM EXTEM and TEG Kaolín with heparinase) because of hemodilution by the prime of the CPB circuit that reduces the platelet and fibrinogen function. This effect is also seen in the test with platelet inhibitor FIBTEM (ROTEM) and functional fibrinogen (TEG), which shows fibrinogen dilution. Platelet dysfunction worsens with CBP duration. During full heparinization on CPB, the trace will be a flat line in tests susceptible to heparin such as INTEM (ROTEM) and Kaolin (TEG). Heparinase is needed to neutralize the heparin effect on CPB, such as HEPTEM (ROTEM) and heparinase (TEG). These testing will also detect the presence of fibrinolysis and its response to treatment. Thromboelastography and thromboelastometry are the gold standards for fibrinolysis diagnosis. The fibrin degradation products and D-dimer (increased in the setting of trauma, tumor, or orthopedic surgery). Fibrinolysis diagnosis is made by the lysis times reviewed previously in this chapter. It can easily be noticed by thinning at the end of the graph. Figure 17 shows a pediatric patient undergoing a heart transplant who developed fibrinolysis.

Post-protamine administration, the comparison between tests with and without heparinase could tell us about the need for additional prot-

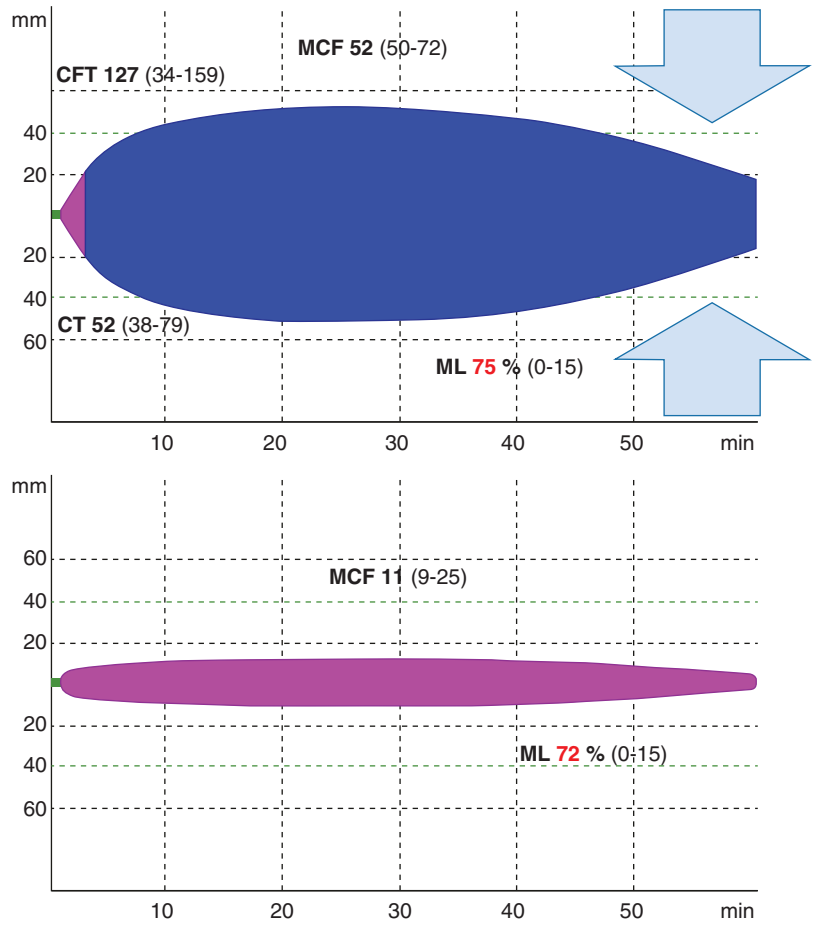

Fig. 17 EXTEM graph (above) and FIBTEM graph (below) showing thinning at the end of the graph (arrows) suggestive of hyperfibrinolysis

amine if the traces are different (Mittermayr et al. 2009). At this time, the need for platelets, fibrinogen, and other blood products needs to be assessed. It must be kept in mind that activated clotting time (ACT) not only depends on heparin administration but is also affected by hemodilution, low platelet count, hypofibrinogenemia, and protamine overdose. Repeated doses of protamine prolong the ACT and cause additional platelet dysfunction. It has been shown that prolonged ACT after protamine administration does not indicate residual heparinization after cardiopulmonary bypass in pediatric open-heart surgery (Yamamoto et al. 2015) and that the thromboelastometric variable, INTEM-CT: HEPTEM-CT ratio, correlated with heparin concentration ($r = 0.72$), but ACT ($r = -0.12$), APTT ($r = 0.36$), and whole blood heparin concentration, determined using the Hepcon HMS, did not (Ichikawa et al. 2014). Usually, protamine is administered far too much to treat bleeding in patients who do not need it. The erroneous approach treats ACT values, not unreversed heparin (Levy and Tanaka 2009).

The European Society of Anesthesiology Guidelines for managing severe perioperative bleeding (Kozek-Langenecker et al. 2013) recommends fibrinogen concentrate infusion guided by POC coagulation monitoring to reduce blood loss in complex cardiovascular surgery (1B level of evidence). In addition, the guideline advocates using fibrinogen concentrate or cryoprecipitate to increase plasma fibrinogen concentrations above trigger values of 1.5–2.0 g/L or FIBTEM MCF > 7 mm in bleeding children (2C).

During the prolonged exposure to artificial surfaces like mechanical valves, artificial hearts, and assist devices, there is a hypercoagulable

Table 9 Protocol of test to be measured in cardiac surgery

Sample times	ROTEM[a]	TEG
Anesthesia (before CPB)	INTEM EXTEM FIBTEM	Kaolin ± Rapid TEG Functional fibrinogen
The late phase of **CPB** (rewarming)	HEPTEM EXTEM FIBTEM	Heparinase ± Rapid TEG Functional fibrinogen
10 min after **Protamine**	HEPTEM + INTEM[b]	Kaolin + Heparinase[b] Functional fibrinogen
ICU	FIBTEM EXTEM	± Rapid TEG

If there is suspicion of hyperfibrinolysis: + APTEM
After each treatment: repeat test with abnormal results
Platelet function test (Platelet Mapping or ROTEM Platelet) should be considered in patients who recently used aspirin and P_2Y_{12} antagonists
[a]This recommendation is based on liquid ROTEM delta and ROTEM sigma reagents. The heparin sensitive single-use reagents FIB-TEM S, EX-TEM S, and AP-TEM S are not used for testing during CPB
[b]CT_{INTEM}/CT_{HEPTEM} or Kaolin/Heparinase = 1.0 for optimizing heparin neutralization

state beyond the CPB period. This continuous exposure enhanced by turbulent flows activates platelets causing white thrombi. In addition, if the intrinsic and extrinsic coagulation pathways are activated, red thrombi can also be produced. Extensive thrombi can obstruct the flow to vital organs and, if fragmented, can embolize distally. To prevent the hypercoagulable state, this patient population requires anticoagulant and antiaggregant therapy monitored by thromboelastogram and platelet function. Heparin anticoagulation increases the R-value, and platelet function inhibition is adjusted with specific testing.

ROTEM and TEG have developed an algorithm to be used in cardiac surgery and are summarized in Table 9:

Clinical guidelines by the Society of Thoracic Surgeons and the Society of Cardiovascular Anesthesiologist published in 2007 address the need for bedside coagulation monitoring to guide blood products administration. Through the guideline, there is a discussion about the validity of methods and algorithms to guide blood and blood product use. In Chap. 7, reviewing the use of ROTEM and TEG for bedside monitoring of hemostasis and decreased blood product in cardiac surgery, the level of evidence was A (based on prospective randomized studies). In June 2008, NHS. Quality Improvement Scotland published recommendations regarding the effectiveness of ROTEM and TEG. This report was built with a health technology assessment tool, which reviews the evidence base in four aspects:

1. Clinical effectiveness: the report concluded that viscoelastic testing reduces the number of blood transfusions, complications, and infections from remote clinical management.
2. Costs and benefits: improve quality of life and are cost-effective. For example, ROTEM and TEG, even though more expensive than traditional testing but save blood, blood product administration, hospital stay, and short- and long-term complications.
3. Organizing aspects: differences exist in the way different hospitals use ROTEM and TEG.
4. Patients' benefit avoiding transfusion is welcomed by patients.

Based on this evidence, the NHS Quality Improvement Scotland recommended the use of ROTEM and TEG instead of traditional coagulation testing to identify bleeding during or after cardiac surgery or liver transplant (Craig et al. 2008).

The publications show a reduction of blood product use in cardiac surgery guided by thromboelastogram or thromboelastometry algorithm versus the use of clinical judgment and traditional testing (Nuttall et al. 2001; Agarwal et al. 2015a, b). In addition, there is a reduction in the surgical re-exploration in cardiac surgery once thromboelastography has been introduced in clinical practice (Spiess et al. 1995).

Individualized goal-directed hemostatic therapy seems to be a safer and most effective approach to stop bleeding in cardiac surgery. The POC algorithm guided by thromboelastometry and whole-blood impedance aggregometry based in first-line therapy with fibrinogen and prothrombin complex has reduced the use of blood transfusion. It has also reduced the incidence of thrombotic/thromboembolic, transfusion-related adverse events, cost, and improved patient outcomes (Görlinger et al. 2013b). Furthermore, a

NICE (National Institute for Health and Care Excellence, UK) diagnostics guideline recommends viscoelastic devices (ROTEM and TEG) to help monitor blood clotting during and after cardiac surgery. The use of viscoelastometric POC testing devices was shown to be "associated with lower mortality, a reduced probability of experiencing complications, and less transfusion and hospitalization" (NICE 2014). Furthermore, when coagulopathy is suspected, the American Society of Anesthesiologists (ASA) advocates the use of POC testing devices to identify and treat the cause of bleeding (ASA 2015); the European Society of Anesthesiology in the first update of the guidelines in management of severe perioperative bleeding (Kozek-Langenecker et al. 2017) recommend the use of standardized VHA-guided hemostatic algorithms with predefined intervention triggers, and the Hemostasis and Transfusion Scientific Subcommittee of the European Association of Cardiothoracic Anesthesiology in an international consensus statement (Erdoes et al. 2019) recommends the assessment of fibrinogen activity using viscoelastic point-of-care testing shortly before or after weaning from cardiopulmonary bypass in patients and procedures with a high risk of bleeding, in contrast with the use of Clauss fibrinogen test that cannot be longer recommended without restrictions due to its long turnaround time, high inter-assay variability and interference with high heparin levels and fibrin degradation products.

Görlinger et al. (2013a, b, in a large retrospective study with 14,162 ROTEM assays from adults undergoing non-cardiac surgery, observed that early values of clot firmness, measured as soon as 5 min after clotting time, were strongly correlated ($r > 0.9$) with the maximum clot firmness (MCF). Dirkmann et al. (2013), in another study on 437 ROTEM analysis of adults undergoing cardiac surgery on CPB, confirmed the strong correlations between A5, A10, A15, and MCF, both before and after protamine administration. Finally, Perez-Ferrer et al. (2015), in a large multicenter retrospective study, analyzed 4762 ROTEM in children undergoing cardiac or non-cardiac surgeries, demonstrating a strong correlation between early values of clot amplitudes (e.g., A5, A10, A15) and maximum clot firmness (MCF). These results confirmed that early thromboelastometry parameters (e.g., 5 min after clotting time) allow an early goal-directed hemostatic therapy in bleeding children. Nakayama et al. (2015), in 100 pediatric cardiac patients, using early thromboelastometric variables (EXTEM-A10 and INTEM-A10) in the ROTEM algorithm and comparing with conventional care, reduced bleeding, red cell transfusion, and critical care duration.

The number of patients treated with antiplatelet drugs due to cardiovascular disease continuously increases, even in pediatric patients. New ADP receptor antagonists are being developed with different pharmacokinetics and pharmacodynamics profiles which its effects need to be assessed. POC testing may be desired to guide a bridging protocol when one or two antiplatelet drugs are discontinued. Moreover, patients not responding to antiplatelet medications can be identified. However, some institutions treat these patients without using these devices, and the standard of care must be determined yet (Theusinger et al. 2015). Finally, POC testing allows monitoring the hemostasis, one of the most problematic aspects of any surgery. Global coagulation testing run at the bedside (e.g., operation room and ICU) allows managing ongoing coagulopathy.

Despite numerous guidelines and consensus statements for patient blood management in cardiac surgery, research has revealed that adherence to these guidelines is poor. As a result, significant variability in patient transfusion practices among practitioners remains. A recent publication of the Society of Cardiovascular Anesthesiologists, the Clinical Practice Improvement Advisory for Management of Perioperative Bleeding and Hemostasis in Cardiac Surgery patients, includes the summary statements and algorithms designed by the working Group guided by POC coagulation monitors (Raphael et al. 2019).

The implementation of POC-based algorithm-guided hemostatic therapy reduced blood and blood component therapy exposure in a prospective randomized clinical trial (Nakayama et al. 2015). In addition, it was associated with a reduc-

tion of the duration of mechanical ventilation, ICU, and hospital stay in pediatric congenital cyanotic surgical patients (Karanjkar et al. 2020).

Fibrinogen level is independently associated with severe bleeding in low-weight children undergoing cardiac surgery (Ranucci et al. 2019). In addition, POC tests are valid methods for predicting hypofibrinogenemia before separation from the CPB (Karkouti et al. 2013; Mace et al. 2016) without increasing adverse outcomes (Erdoes et al. 2019).

In the massively bleeding coagulopathic patient, a European consensus statement in cardiac and non-cardiac surgical patients recommends the administration of four-factor prothrombin complex concentrate (PCC) that can be guided by POC test (Erdoes et al. 2021).

The use of POC devices integrated into evidence-based algorithms is one of the essential mechanisms to limit blood product exposure, avoiding transfusions adverse events. In addition, POC-based algorithms allow goal-directed transfusions of blood products and better-targeted factor concentrate substitutions.

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Preoperative Evaluation

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Abstract

Evaluation of the patient with congenital cardiac lesion consists of a complete understanding of the anatomical detail of the lesion as well as its pathophysiological impact. To achieve this goal, the clinician should first gather information from medical history, physical examination, and paraclinical studies; this includes a sophisticated detailed preoperative evaluation.

In this chapter, the preoperative evaluation is discussed mainly under the following subtitles using sequential steps of a rational preoperative evaluation in patients with congenital cardiac disease:

- Medical History.
- Physical Examination.
- Paraclinical Diagnostic Tests including chest radiography, electrocardiography; echocardiography, computerized tomography, cardiac magnetic resonance imaging (cMRI), cardiac catheterization & angiography, central nervous system assessment.

Scientific analysis of information gathered from medical history, physical examination, and diagnostic tests could guide the surgeon to choose the best management plan.

Keywords

Medical history · physical examination paraclinical test · diagnostic test · Congenital cardiac lesion · Congenital heart disease

Introduction

Evaluation of the patient with congenital cardiac lesion consists of a complete understanding of the anatomical detail of the lesion as well as its pathophysiological impact. To achieve this goal, the clinician should first gather information from medical history, physical examination, and paraclinical studies. Then, he or she can interpret the patient's information in the context of making an accurate diagnosis (Davey et al. 2021). This chapter describes sequential steps of a rational preoperative evaluation in patients with congenital cardiac disease.

Medical History

The first step for the approach to the patient suspected of having congenital heart disease is a thorough medical history. Data collection should be returned to the fetal life (Davey et al. 2021).

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Some information related to the mother's pregnancy could be very important. For example, infants born of mothers with diabetes mellitus may have different kinds of congenital heart defects (Rowland et al. 1973; Ornoy et al. 2021). According to one study, the incidence of congenital heart disease in this group is 4%, which is five times the incidence in the general population (Mace et al. 1979). The defects are of a wide variety, but the most common lesion is the transposition of the great arteries (Driscoll et al. 1960). The history of maternal systemic lupus erythematosus is also important because of its association with congenital cardiac disorders in the fetus (Lateef and Petri 2017; Pastore et al. 2019; Diaz-Frias and Badri 2021). Other maternal historical notes which are of diagnostic importance are rubella syndrome babies, premature infants, and children who were born and lived at high altitudes. In all three situations, patent ductus arteriosus is possible (Singh et al. 2017; Shukla and Maraqa 2021).

A history of maternal exposure to alcohol or drugs may provide a clue to diagnose the cardiac defect. A variety of drugs may cause different types of malformations in the offspring. The physician should also ask about perinatal history that includes premature rupture of membrane, gestational age and APGAR score, asphyxia, and cyanosis at birth, and any defects (even not heart-related) diagnosed at birth (Moss 1992; Iftikhar and Biswas 2021).

Another aspect of history taking is family history. The presence of congenital heart disease in a first-degree relative may be very important. According to Nora, the recurrence rate in a first-degree relative is 1% to 4% (Nora 1968; Nora and Nora 1976). The atrial septal defect, Tetralogy of Fallot, ventricular septal defect, and patent ductus arteriosus are the most recurring lesions (Peyvandi et al. 2014).

Now the physician should focus on the patient's condition. The growth and development of the child should be considered very carefully. Height and weight gain can be affected by poor cardiac function, pulmonary edema, or left to right shunt.

Inappropriate sweating has been frequently seen in infants with large left to right shunts. It is generally accepted that inappropriate sweating in an infant, particularly while feeding, is a reliable sign of overt or impending heart failure.

Syncope of cardiac origin is relatively rare in infants and children. When it occurs, it is almost always due to an arrhythmia (Környei et al. 2021).

Endurance and exercise tolerance may be affected by underlying cardiac diseases, especially those involving obstructive lesions such as aortic and pulmonic stenosis.

Chest pain may be a symptom of congenital heart disease in children, although it is not common. The pain character can be atypical. It is usually induced by effort, but it can occur at rest. Aortic stenosis, pulmonic stenosis, mitral valve prolapse, and primary pulmonary hypertension are some congenital cardiac causes of chest discomfort (Selbst et al. 1990).

In the past, a history of squatting was very common in patients with the Tetralogy of Fallot. Nowadays, this sign has been found infrequently.

Also, the physician should ask about palpitation. This can suggest sinus tachycardia, supraventricular or ventricular arrhythmia, and other irregular rhythms.

Physical Examination

Each examiner should follow five steps to perform a complete cardiac physical examination: vital signs, inspection, palpation, percussion, and auscultation.

The first step is vital signs assessment. Heart rate and respiratory rate changes can be the first clues of myocardial failure, pulmonary congestion, or arrhythmia, well before changes in blood pressure occur. On the initial visit, blood pressures should be measured in both upper extremities and one lower extremity. Blood pressure measurement in young infants is achieved by following a special maneuver (Cobben et al. 2014; Strobel and Lu le 2015; Thomas and Battle 2015).

Also, the blood pressure in children should be matched with age (Tables 1 and 2).

Each patient should be inspected for general appearance, nutritional status, skin color, and any kind of discomfort. All of the above-mentioned items may be very important in the diagnosis of underlying disease.

Cyanosis could be an important sign of cardiac lesion. It is categorized as peripheral and central cyanosis. Central cyanosis, which is due to the lesions of the lungs or the heart, involves the skin and the mucosa, in contrast to peripheral cyanosis; however, the clinician should differentiate between central, peripheral, and differential cyanosis (Pahal and Goyal 2021). The differentiating point between pulmonary cyanosis and cardiac cyanosis is that the first diminishes with oxygen and crying (Adeyinka and Kondamudi 2021). Cyanosis is clinically detectable when arterial saturation is less than 80% to 85% unless the patient is anemic. Cyanosis is a helpful clue because it places the defect within the cyanotic group of heart diseases (Moss 1992). The age at which cyanosis is first observed has important diagnostic implications. For example, most neonates with transposition of great arteries have obvious cyanosis in the first days of life, but in the tetralogy of Fallot, cyanosis may be delayed for weeks or months (Levin et al. 1977).

Palpation is one of the most important parts of physical examination. Peripheral pulses, the chest, the abdomen, and the back should be palpated in each cardiac examination. Visible or palpable pulsations sometimes provide a helpful clue to diagnosis, for example, pulsations in the suprasternal notch can occur with aortic stenosis or insufficiency (Dewaswala and Chait 2021). On the other hand, diminished pulsation in the lower extremity is the hallmark of coarctation (Zimmerman and Williams 2021).

Percussion is primarily used to evaluate the total span of the liver. Chest percussion can detect pulmonary consolidation or effusion.

Table 1 Normal range of blood pressure in ***BOYS*** with especial focus on "**The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**" of the "**National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents**"

	DBP mmHg		SBP mmHg		MAP mmHg	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	34–39	54–58	80–89	98–106	49–55	69–75
2	39–44	59–63	84–92	101–110	54–60	73–79
3	44–48	63–67	86–95	104–112	58–64	77–82
4	47–52	66–71	88–97	106–115	61–67	79–86
5	50–55	69–74	90–98	108–116	63–69	82–88
6	53–57	72–76	91–100	109–117	66–71	84–90
7	55–59	74–78	92–101	110–119	67–73	86–92
8	56–61	75–80	94–102	111–120	69–75	87–93
9	57–62	76–81	95–104	113–121	70–76	88–94
10	58–63	77–82	97–106	115–123	71–77	90–96
11	59–63	78–82	99–107	117–125	72–78	91–97
12	59–64	78–83	101–110	119–127	73–79	92–98
13	60–64	79–83	104–112	121–130	75–80	93–99
14	60–65	80–84	106–115	124–132	76–82	95–100
15	61–66	81–85	109–117	126–135	77–83	96–102
16	63–67	82–87	111–120	129–137	79–85	98–104
17	65–70	84–89	114–122	131–140	81–87	100–106

Modified from "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management." Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp. 65–116. Published with kind permission of © Springer Nature, 2017. All Rights Reserved (McLain 1976; Blumenthal et al. 1977; Horan and Sinaiko 1987; Feld and Springate 1988; Brzezinski 1990; Zubrow et al. 1995; Bartosh and Aronson 1999; 2004; Dionne et al. 2012; Bonafide et al. 2013; Heys et al. 2013; Shieh et al. 2013; Bassareo and Mercuro 2014; Ingelfinger 2014; Shah et al. 2015; Herbert et al. 2020)

Table 2 Normal range of blood pressure in *GIRLS* with especial focus on "**The Fourth Report on the Diagnosis, Evaluation, and Treatment of High Blood Pressure in Children and Adolescents**" of the "**National High Blood Pressure Education Program Working Group on High Blood Pressure in Children and Adolescents**"

	DBP mmHg		SBP mmHg		MAP mmHg	
Age (year)	50% DBP	95% DBP	50% SBP	95% SBP	50% MAP	95% MAP
1	38–42	56–60	83–90	100–107	53–58	71–76
2	43–47	61–65	85–91	102–109	57–62	75–80
3	47–51	65–69	86–93	104–110	60–66	78–83
4	50–54	68–72	88–94	105–112	63–67	80–85
5	52–56	70–74	89–96	106–114	64–69	82–87
6	54–58	72–76	91–98	108–115	66–71	84–89
7	55–59	73–77	92–101	110–119	67–73	85–91
8	57–60	75–78	94–102	111–120	69–74	87–92
9	58–61	76–79	95–104	113–121	70–75	88–93
10	59–62	77–80	97–106	115–123	72–77	90–94
11	60–63	78–81	99–107	117–125	73–78	91–96
12	61–64	79–82	102–109	119–126	75–79	92–97
13	62–65	80–83	104–110	121–128	76–80	94–98
14	63–66	81–84	106–112	123–129	77–81	95–99
15	64–67	82–85	107–113	124–131	78–82	96–100
16	64–68	82–86	108–114	125–132	79–83	96–101
17	64–68	82–86	108–115	125–132	81–84	96–101

Modified from "Congenital Heart Disease in Pediatric and Adult Patients; Anesthetic and Perioperative Management." Dabbagh A., Hernandez Conte A., Lubin L. Springer 2017, pp. 65-116. Published with kind permission of © Springer Nature, 2017. All Rights Reserved (McLain 1976; Blumenthal et al. 1977; Horan and Sinaiko 1987; Feld and Springate 1988; Brzezinski 1990; Zubrow et al. 1995; Bartosh and Aronson 1999; 2004; Dionne et al. 2012; Heys et al. 2013; Bassareo and Mercuro 2014; Ingelfinger 2014; Shah et al. 2015; Herbert et al. 2020; Erickson et al. 2021)

Auscultation is the final and probably most important step in physical examination. The examiner should recognize heart sounds and describe murmurs in terms of location, timing, severity, and radiation. The analysis of auscultation findings may lead to the diagnosis of a heart lesion.

The signs of congestive heart failure should be sought. These include pallor, sweating, cool extremities, tachypnea, tachycardia, jugular venous distention, hepatomegaly, edema, and ascites.

The association between cardiac defects and some genetic syndromes should be considered. The knowledge that some specific heart lesions predominate in some syndromes helps to provide the diagnosis (Grifka 1999; Edwards and Gelb 2016; Pierpont et al. 2018; Yasuhara and Garg 2021). However, novel personalized diagnostics improve our knowledge to diagnose so early and to detect the risk of the disease; in such a way that preventive measures are more meaningful in congenital heart patients (Xu et al. 2018; Napoli et al. 2019; Diz et al. 2021; Dyer and Rugonyi 2021).

Timing of signs and symptoms: age at which a murmur first appears can be helpful in diagnosis. The murmur of a ventricular septal defect is not audible at birth. It may be delayed for several hours to a few weeks.

Cardiac failure due to a congenital heart defect occurs mainly during infancy. At a given age, certain defects predominate. Thus, the age when heart failure begins is a helpful clue to diagnosis (Moss 1992).

Central Nervous System Assessment

Central Nervous System (CNS) related concerns are among the most important challenges in the congenital heart disease patients, not only due to the effects of the cardiovascular system on the prenatal and antenatal growth and development of CNS but also due to the associated congenital

CNS anomalies. Add to the latter, the untoward effects of the perioperative period on the CNS. A thorough and sophisticated preoperative CNS evaluation is an integral part of the preoperative care, which should be completed with necessary perioperative CNS monitoring; for further discussions, the interested reader is referred to Chap. 11 (Central Nervous System Monitoring in Pediatric Cardiac Surgery) and Chap. 44 (Postoperative Central Nervous System Management in Congenital Cardiac Surgical Patients).

Paraclinical Diagnostic Tests

Chest Radiography

Chest X-Ray is a useful diagnostic tool in the evaluation of patients with congenital heart disease. Abdominal situs, the position of the aortic arch, size and shape of the cardiac silhouette, and pulmonary vascularity are all important clues in the evaluation of a patient suspected of having a congenital cardiac anomaly.

The position of the cardiac apex, stomach bubble, and liver determine the splanchnic situs of the patient. Isolated dextrocardia is often associated with congenital heart disease, while situs inversus totalis has a low incidence of cardiac anomalies (Jacobs 2015).

The cardiac shape has some clues to the underlying pathophysiological defects. Cardiomegaly is seen with volume loading lesions or valvular insufficiency. Some specific features implicate specific disorders; for example a boot shape heart is typically seen in patients with Tetralogy of Fallot, or a narrow mediastinum is characteristic of transposition of great arteries (TGA) because of the anteroposterior orientation of the aorta and pulmonary artery.

Consideration of pulmonary vascularity is also very important while evaluating chest radiography. Left-to-right shunts result in cardiomegaly and increased pulmonary vascularity. On the other hand, cyanotic lesions with a component of pulmonary stenosis show decreased pulmonary vascular markings. Features of pulmonary edema are seen in left-sided heart failure or obstruction in the pulmonary venous pathway (i.e., obstructive total anomalous pulmonary venous connection).

Electrocardiography

Electrocardiography (ECG) is one of the important steps in preoperative evaluation. The clinician should follow a systematic approach for the evaluation of ECG. It means that the items listed below should be evaluated sequentially: Heart Rate, Heart Rhythm, Axis, and Intervals (PR, QRS…). Then, size and shape and any changes of specific waves (P- R- Q- T) should be considered.

The enlargement or hypertrophy of cardiac chambers, dysrhythmia, and ischemic changes which are shown in the patient's ECG could provide helpful clues for the diagnosis or the degree of progression of the cardiac lesion (Baik et al. 2015; Gorges et al. 2015).

The audience is suggested to refer to Chaps. 11 and 44 (Central Nervous System Monitoring in Pediatric Cardiac Surgery and Postoperative Central Nervous System Management in Congenital Cardiac Surgical Patients) of this book for more detailed discussions about ECG.

Echocardiography

Today, the accuracy of echocardiography as the sole method of preoperative anatomic evaluation is validated. Full anatomic details should be delineated before surgery for appropriate planning. A complete echocardiographic report consists of atrial situs, looping of ventricles, atrioventricular and ventriculoarterial concordance or discordance, the position and intactness of the atrial and ventricular septa, inflow and outflow tracts of ventricles, the function of ventricles, shape, and function of atrioventricular and ventriculoarterial valves, the anatomy of venae cavae, pulmonary veins and aorta. The changes due to previous operations should also be evaluated (Marek et al. 1995).

Transesophageal echocardiography is a valuable means for evaluating patients, not only in the operating room but also in the intensive care units. It is useful for obtaining further details of complex congenital heart lesions and assessing postoperative results (Bengur et al. 1998; Stevenson 2003; Kamra et al. 2011).

Computerized Tomography

Multislice computerized tomography has provided images with very high resolution. This test could be performed extremely fast. Computed tomography can be used for anatomic evaluation and three-dimensional reconstruction of cardiac and extra-cardiac structures.

The short acquisition time and the obviation of the need for sedation are advantages compared with MRI; however, there are concerns with radiation exposure and the use of nephrotoxic contrast agents (Einstein 2009).

Cardiac Magnetic Resonance Imaging (cMRI)

Cardiac MRI can be utilized as an imaging modality when a specific anatomic and functional study is needed. It provides detailed information about the cardiac structure, especially in patients with complex congenital lesions. It can be used to evaluate intra-cardiac shunts and quantify ventricular volumes. The need for sedation in young children and the inability to use in the presence of metal implants are the limitations of cardiac MRI (Constantine et al. 2004; Rajiah et al. 2017). Also, quantitative analysis methods improve the quality of data gained from cMRI. However, there are novel alternatives to match cMRI data with "computer modeling, 3D printing, and other methods" so we could assess the anatomic and physiologic abnormalities in a more sophisticated method in congenital heart disease (Rajiah et al. 2017). Meanwhile, a detailed assessment of postoperative results could be performed using novel technologies (Mohamed et al. 2020; Ramirez-Suarez et al. 2021). Meanwhile, data gained from machine learning applications, deep learning, and support vector machine especially considering their algorithms significantly improve the outcome in congenital heart disease (Helman et al. 2021).

Cardiac Catheterization and Angiography

The role of cardiac catheterization and angiography as a diagnostic tool has changed during the past decades. Today, the indications of catheterization are limited. The three major indications for performing a cardiac catheterization are the following:

- A complete anatomic diagnosis or necessary hemodynamic information cannot be obtained by noninvasive methods.
- Clinical signs and symptoms are not consistent with a patient's diagnosis.
- A patient's clinical course is not progressing as expected.

Anticipatory preparation for all catheterizations must include a complete history, review of all previous cardiac catheterizations and surgeries, physical examination, and review of all pertinent noninvasive studies.

Cardiac catheterization mainly consists of the measurements of different physiologic variables. These include the measurement of pressures, saturation and intra-cardiac shunts, cardiac output, and vascular resistance.

Sometimes cardiac catheterization should be performed as a kind of preoperative intervention. Balloon atrial septostomy may be needed in neonates with transposition of the great arteries to improve intra-cardiac mixing and thus tissue oxygenation. Patients with pulmonary atresia, ventricular septal defect, and multiple aortopulmonary collaterals may also undergo preoperative cardiac catheterization to determine the anatomy of their collateral flow and whether they can be occluded before surgery (El-Said et al. 2000; Rutledge et al. 2002; Carlson et al. 2005; Grifka et al. 2008; Butera et al. 2015; Rihal et al.

2015a, 2015b). The detailed discussions about these topics could be found in Chap. 5 (Perioperative Care of the Congenital Cardiac Patient in the Cardiac Catheterization Laboratory) of this book.

Conclusion

The art of making an accurate diagnosis and appropriate surgical planning demands a meticulous preoperative evaluation. This process consists of definitive components; each of them has its specific importance. Scientific analysis of information gathered from medical history, physical examination, and diagnostic tests could guide the surgeon to choose the best management plan.

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Multi-Systemic Consequences of CHD and the Impact on Perioperative Care

Lorraine N. Lubin

Abstract

The quality of life and overall life expectancy for patients with congenital heart disease (CHD) have significantly improved over the past 30 years. This represents an enormous milestone for these patients who have successfully advanced from childhood to adulthood with increasing numbers. The current improved survival of the CHD patient population has resulted in a profound epidemiologic shift resulting in the growing ACHD population. This ever-evolving patient population faces the risk of acquiring chronic multi-systemic disease which begins to develop in early childhood as a result of their congenital cardiac anatomy, hemodynamic impact, and unique physiology (Warnes et al., Circulation 118:e714–e833, 2008). These comorbidities, which are a result of the CHD patient's unique physiology significantly, contribute to the morbidity and mortality of patients with CHD (Fig. 1). Diminished survival has been documented among patients with CHD due to restrictive lung disease, renal dysfunction, cirrhosis, anemia, pulmonary hypertension, infection, endocrine abnormalities, immunological perturbations, psychosocial conditions, and malignancy (Afilalo et al., J Am Coll Cardiol 58:1509–1515, 2011). In addition to the sequelae of their CHD the ACHD patient is also at risk for acquired, age-related comorbidities. The consequences of life-long health challenges also take a toll on this population with psychosocial and cognitive developmental impact which is pervasive among this population and has significant impact on the quality of life of the CHD patient (Roche and Silversides, Can J Cardiol 29:841–848, 2013). Incumbent upon the physicians caring for this special group of patients is the appreciation of the CHD patients' unique physiology and the impact of multi-organ sequelae. Limiting the trauma of lifetime health challenges requires a comprehensive care plan and a special CHD program focused on the unique care of these patients. Future developments will require extensive research regarding potential modifications of care which are targeted at prevention of the multi-systemic end-organ dysfunction.

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Adult congenital heart disease · Multi-systemic consequences · Restrictive lung disease · Fontan-associated liver disease · Protein losing enteropathy · Cardiorenal syndrome · Plastic bronchitis · Hepatocellular carcinoma · Lifetime trauma

The Impact of Multi-Systemic Organ Dysfunction on the CHD Patient

With more than 90% of children with CHD surviving to the median age of 40 years and the number >65 years of age increasing, the adult congenital heart disease (ACHD) population has surpassed the number of pediatric patients with CHD (Figs. 1 and 2).

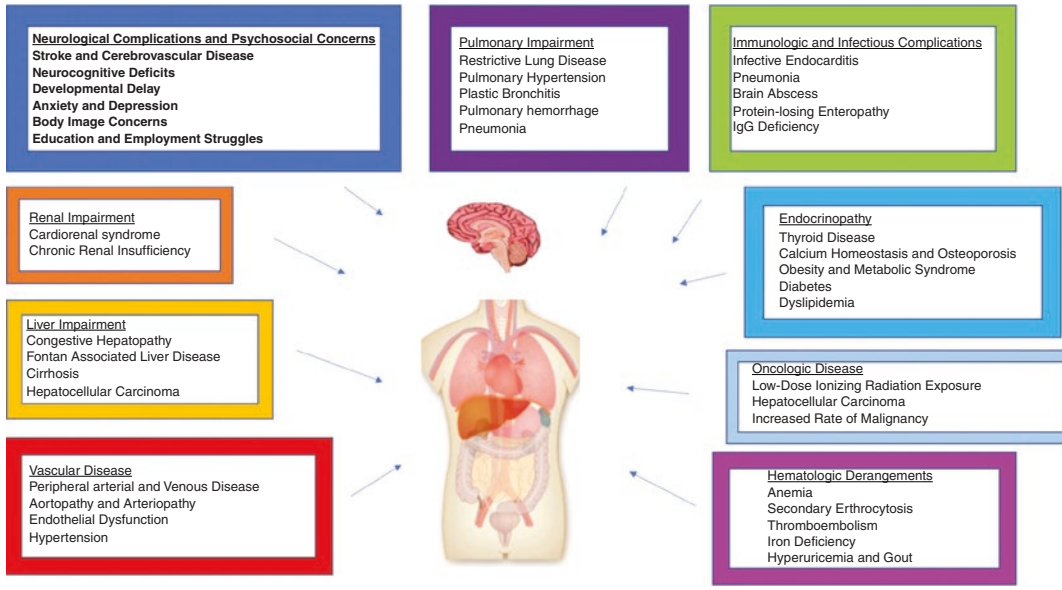


Fig. 1 The multi-systemic organ involvement of congenital heart disease

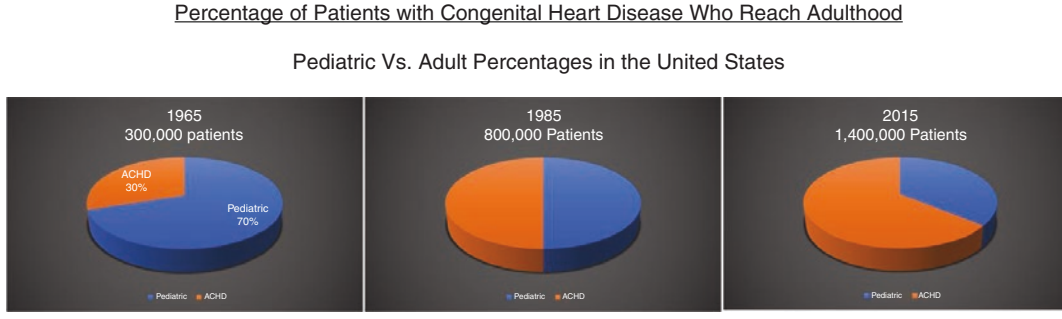


Fig. 2 Data and statistics on congenital heart disease*: Center for Disease Control (CDC).* (*Content source: National center on birth defects and developmental disabilities, CDC Jan. 24, 2022)*

Percentage of Patients with Congenital Heart Disease Who Reach Adulthood

Pediatric Vs. Adult Percentages in the United States

ACHD patients account for more than 60% of CHD patients and the population of these patients in the United States is approximately 1.5 million patients. Epidemiologic studies of CHD patients have recently shown that not only are patients with CHD living longer and in greater numbers, but the complexity of disease among this growing group of patients is increasing exponentially (Khairy et al. 2010). The prevalence of severe CHD has increased by 55% among ACHD patients and includes complicated lesions such as transposition complexes, single ventricle anatomy, pulmonary atresia, and Eisenmenger syndrome. The increase in lifespan of this cohort of patients has resulted in the incidence of adult-onset-related comorbidities such as hypertension, coronary artery disease (CAD), and diabetes mellitus (DM). The consequences of chronically abnormal hemodynamics resulting from palliated CHD and acquired age-related systemic disease places these patients at increased risk for multi-organ dysfunction and may impact long-term survival. In age-matched cohorts, the prevalence of renal impairment and DM is significantly higher in the primary care populations of patients with ACHD versus their peers without CHD.

The abnormal physiology and hemodynamics of CHD cause nearly all major organ systems to manifest significant sequelae and end organ damage. In studies of patients with ACHD, greater than 40% of patients have abnormal pulmonary function tests and more than 50% of ACHD patients have been found to have abnormal glomerular filtration rates (GFR). Patients who have undergone the Fontan procedure and other forms of single ventricle anatomy/physiology develop congestive hepatopathy and hepatic dysfunction which require the ultimate palliation with heart–liver transplantation. CHD is frequently an associated anomaly of genetic syndromes and may have associated neurocognitive, immunologic, and endocrine abnormalities. Patients with Downs' syndrome frequently have associated endocardial cushion defects as their primary form of CHD; however, the non-cardiac causes of death include accelerated Alzheimer disease, strokes, seizures, DM, pneumonia, and malignancy. Patients with cyanotic CHD at all ages have the most significant multi-organ dysfunction, with the body's compensatory mechanisms creating a number of the most pathologic conditions such as polycythemia and other hematological abnormalities. The chronicity and acuity of lifelong CHD and its need for recurrent diagnostic and invasive intervention puts a majority of CHD patients at risk for post-traumatic stress disorder, depression, and other psychological and social challenges. Patients may also experience neurocognitive deficits as a result of concomitant genetic syndromes, strokes, or hypoxic ischemic damage from perioperative insults.

Comorbid non-cardiac conditions have significant impact on perioperative morbidity and mortality for both cardiac and non-cardiac procedures. For patients with ACHD, hepatic dysfunction and chronic pulmonary disease have been shown to place patients at significantly increased perioperative mortality. Compared to the general, age-matched population, the ACHD cohort has significantly increased risk of perioperative complications, mortality, longer hospital stays, and much higher hospital charges compared with the general population. The ACHD population is a high perioperative risk to develop acute renal failure, pneumonia with respiratory failure, deep venous thrombosis (DVT), and pulmonary embolism (PE).

A multidisciplinary patient care team is a necessity for the appropriate management of CHD and ACHD patients. These teams are customarily found in regional tertiary care centers and are comprised of specialized CHD/ACHD cardiologists, hepatologists, pulmonologists, nephrologists, anesthesiologists, immunologists, and specialized cardiac surgical teams. These patients must be monitored for life-long, end-organ dysfunction with preventative strategies to optimize organ function in the peri-procedural setting. After the American College of Cardiology

and the American Heart Association published the ACHD care guidelines, the percentage of ACHD patients receiving care at dedicated, regional ACHD centers increased in California from 46% to 71%. Morbidity and mortality of ACHD patients is lower upon referral to regional ACHD specialized centers where essential, multi-specialty care providers exist along with increase resource allocation aimed at providing comprehensive care. This chapter will focus on the multi-organ sequelae affecting CHD/ACHD patients and its periprocedural impact along with palliative treatment and management strategies. The organ systems most severely and consistently impaired in CHD patients include renal, pulmonary, liver, hematologic, immunologic, endocrine, and vascular systems. CHD and ACHD patients also have significant issues with infections, oncologic and psychosocial conditions.

Renal Disease in the CHD and ACHD Patients

Renal disease is common among patients with all forms of CHD with the most significant dysfunction found in patients with cyanotic ACHD. In a 2008 publication looking at a study cohort of 1102 young ACHD patients in the outpatient setting, 50% of the patients had impaired renal function (Dimopoulos et al. 2008). The cyanotic ACHD patients had a 65% incidence of at least mild renal insufficiency (GFR, 60–89 mL/min^{-1}/1.73 m^{-2}). In this study, significant renal impairment (GFR <60 mL/min^{-1}/1.73 m^{-2}) was seen 18 times more frequently in acyanotic ACHD patients and 35 times more frequently in cyanotic ACHD patients, then age-matched patients without CHD (Lui et al. 2017). The most severely affected group of CHD patients were those with Eisenmenger physiology; this group had an 18% prevalence of renal impairment. Renal dysfunction in patients with CHD also worsens over the lifetime of the patient. In patients with Fontan physiology, there is a 10% incidence of renal impairment at 13 years of age, and this worsens to greater than 50% incidence at approximately 25 years of age. Renal dysfunction is an important perioperative consideration, with worse surgical outcomes noted, as well as increased mortality and rehospitalization rates.

The pathogenesis of renal impairment in CHD patients is multifactorial. The kidneys and heart are connected not only by venous and arterial connections but also by a complex neurohormonal system which modulates hemodynamic parameters such as intravascular volume and blood pressure. There are three major signaling pathways which act on the heart and kidneys. These pathways are the sympathetic nervous system, natriuretic peptides, and the renin–angiotensin–aldosterone system. Acquired renal disease and cardiovascular disease are known to be associated with disease states such as hypertension, diabetes, and atherosclerotic heart disease. These coexisting disease states frequently lead to chronic renal disease and are further delineated into cardiorenal syndromes. The most common cardiorenal syndrome is type two and occurs in 63% of patients with congestive heart failure admitted to the hospital. Cardiorenal syndrome type 2 occurs due to chronic low cardiac output, impaired renal perfusion, and kidney venous congestion. There are five described cardiorenal syndromes of which ACHD patients generally fall into the type two classification of chronic heart failure resulting in chronic kidney disease (CKD). The low cardiac output state and decreased renal perfusion trigger the activation of neurohormonal pathways that lead to impaired kidney autoregulation. The pathophysiologic hemodynamics of congestive heart failure result in both organ systems being impaired with decreased cardiac output and elevated venous pressures leading to a similar state of neurohormonal dysregulation and a cycle of decreased function and worsening disease. The CHD population has a cycle of acute kidney disease on top of chronic kidney disease. This process is a result of repeated procedures in which contrast exposure occurs or cardiopulmonary bypass exposure which causes hypoxic-ischemic injury. Intermittent exposure to nephrotoxic medications and prerenal states in conjunction with chronic CHF and CKD leads to further renal injury and progressive failure.

CHD and renal anomalies frequently occur as part of a syndrome such as VACTERL association and CHARGE syndrome. VACTERL consists of vertebral anomalies, anal atresia, cardiac defects, trachea-esophageal fistula, renal defects, and limb abnormalities. CHARGE consists of coloboma of the eye, heart defects, choanal atresia, growth retardation/developmental delay, and ear anomalies. Retrospective review of the association between cardiac anomalies and renal anomalies showed that approximately 30% of patients with CHD have concomitant renal anomalies. The multi-system work-up of complex CHD includes screening for renal anomalies. The most common renal anomalies found in children with CHD include hydronephrosis/ureteropelvic junction obstruction, vesicoureteral reflux, duplicated collecting systems, and renal agenesis.

Patients with cyanotic CHD have multiple reasons for developing CKD. Chronic hypoxemia causes early renal tubular damage and polycythemia with microcytic anemia creates injury due to increased blood viscosity with poorly deformable microcytes having inadequate oxygen-carrying capacity and resultant renal tissue hypoxia. The increased blood viscosity causes glomerular capillaries to become engorged and ultimately become sclerotic (Fig. 3). The resorption of solutes and electrolytes is impaired leading to altered oncotic pressure dynamics and inappropriate fluid retention. Due to altered urate clearance, patients develop hyperuricemia. The altered osmotic gradient and significant glomerular sclerosis lead to clinically important microalbuminuria/proteinuria which is coexisting with azotemia. The development of significant proteinuria leads to severe consequences such as a hypercoagulable state and thromboembolic complications such as deep venous thrombosis (DVT), pulmonary embolism (PE), and thrombosis of shunts and conduits. Patients with cyanotic CHD are also at risk of developing an acquired, secondary renal tubular acidosis with a normal anion gap.

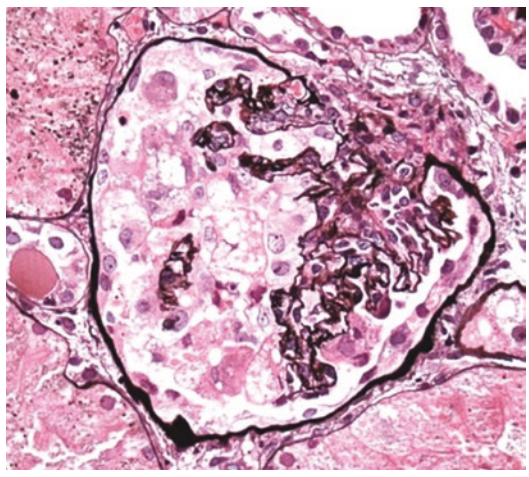


Fig. 3 Glomerular sclerosis in CHD

Management of Renal Impairment in CHD

Due to the prevalence of renal impairment in patients with CHD and its association with increased risk of morbidity and mortality, it is imperative for routine monitoring of renal function to part of ACHD care with assessments preformed at regular intervals and during any period of acute hemodynamic stress. Pre- and post-procedural assessments are also recommended for patients with documented CKD. The assessment of renal function by calculation of GFR relies on serum creatine, age, gender, and race. Normal GFR is considered as >90 mL/min. Patients with impaired renal function, especially those with cyanotic CHD and Eisenmenger physiology, should be referred to a nephrologist and closely monitored. In addition to monitoring GFR, a urinalysis should be performed to assess for proteinuria with a protein to creatine ratio. The periprocedural use of nephrotoxic medications should be avoided in conjunction with IV contrast and prerenal states should be avoided. Commonly used medications such as non-steroidal anti-inflammatory medications, diuretics, antibiotics, anti-arrhythmic medications, and angiotensin-converting enzymes inhibitors are among the most common medications known to impair renal function in CHD patients in the periprocedural period. Patients with CHD should have post-contrast procedure monitoring for renal injury. Perioperative multidisciplinary

planning conferences can improve outcomes in these patients with respect to anticipating contrast loads, volume loads, NPO status, and prerenal propensity and minimizing exposure to nephrotoxic medications. Renal protection with perioperative hydration may decrease the incidence of prerenal states and potential deleterious impact on patient.

Liver Impairment in CHD

The incidence of liver dysfunction among patients with CHD is difficult to assess due to the frequent subclinical nature and in many cases may go undiagnosed. The incidence and extent of disease varies greatly in the CHD population secondary to the variation in anatomy and physiology. The best described liver pathology among the ACHD population is Fontan-associated liver disease (FALD). The histopathology in Fontan/single ventricle physiology has consistently shown in all stages of the disease to have bridging fibrosis as its main pathology. Approximately, 67% of patients with single ventricle physiology will have abnormalities seen on ultrasound. 70–100% of patients will have abnormalities observed on CT scan and MRI imaging. The monitoring of liver disease in Fontan and other single ventricle patients is part of the recommended guidelines described on behalf of the American Heart Association ACHD Committee.

The manifestations of liver disease associated with CHD can range from mild congestive hepatopathy, fibrosis with nodular regeneration, cirrhosis, and even hepatocellular carcinoma (Fig. 4). The Abernethy malformation is a rare congenital portosystemic shunt that has been shown to be associated with CHD in 22% of cases especially in association with polysplenia or left isomerism. Abernethy malformation may present with elevated ammonia levels, hepatic

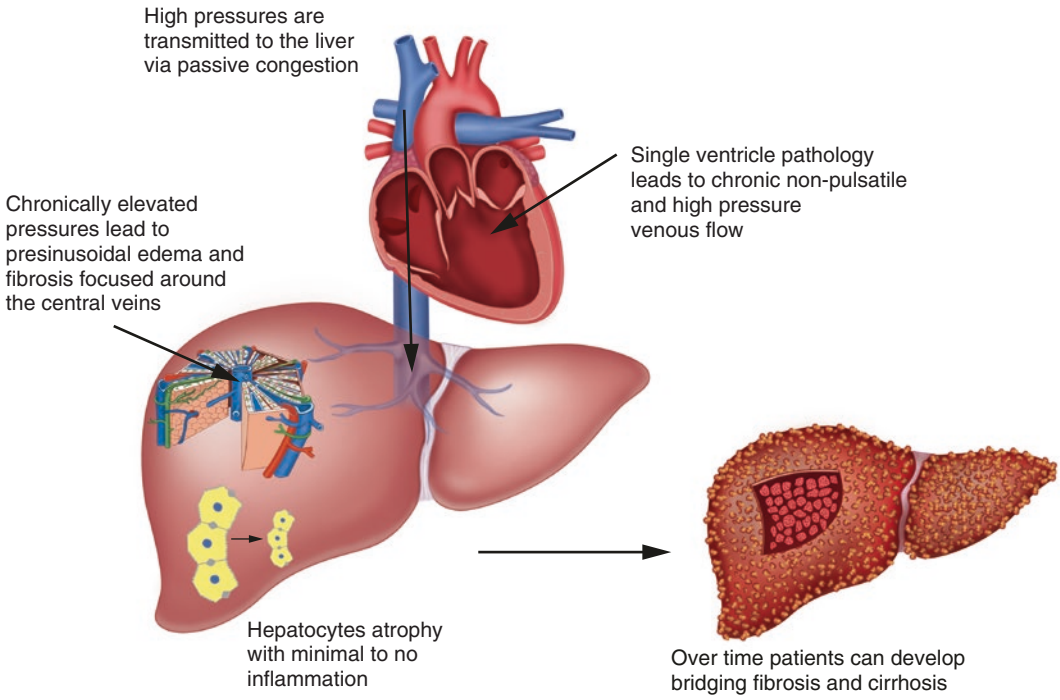


Fig. 4 Congestive hepatopathy pathophysiology in Fontan-associated liver disease (FALD). (*Lemmer* et al. *Differentiating congestion from fibrosis, CLINICAL LIVER DISEASE, VOL 10, NO 6, DECEMBER 2017*)

encephalopathy, nodular liver lesions, and hepatocellular carcinoma. A form of congenital cholestatic liver disease is known as Alagille's syndrome and is associated with pulmonary stenosis, Tetralogy of Fallot, pulmonary atresia, and coarctation of the aorta. Alagille's syndrome is the most common congenital liver disease associated with CHD and occurs in approximately 1 in 40,000 live births. Liver transplantation is occasionally necessary in Alagille's syndrome.

The pathogenesis of liver disease in patients with CHD is basically divided into liver disease caused by hemodynamic abnormalities which cause congestive hepatopathy with ischemia and the second category which is related to toxic exposures and infection. The unique circulation of the liver creates the vulnerability to abnormal hemodynamics and chronic hypoxia. Up to 70% of the liver's blood supply contains significant nutrients but minimal oxygen from the portal venous system and splanchnic circulation. The circulation of the liver flows from the hepatic arterioles and portal venules to the sinusoids and to the central veins. The central veins then merge and drain into the inferior vena cava. In the sinusoids, the nutrients and oxygen are extracted. Therefore, the liver parenchyma nearest to the central veins receives the lowest oxygen content and is prone to ischemic and congestive injury.

The combination of liver congestion related to high central venous pressures, decreased hepatic flow, and chronic hypoxia has been shown to cause liver injury in patients with CHD. When patients without CHD were studied with low cardiac output syndromes, the same disease patterns were not seen. The Fontan circulation is the best example of this pattern of liver disease. Other forms of CHD that exemplify this type of injury are Ebstein's anomaly with severe tricuspid regurgitation, TOF with residual pulmonary insufficiency, D-TGA with obstructed systemic venous baffles, and Eisenmenger's syndrome with severe right heart failure. Patients with CHD can also have severe left heart failure and experience similar liver injury due to elevated pulmonary artery pressures and resulting elevated central venous pressures. Cyanotic CHD results in reactive polycythemia which causes sluggish flow in the hepatic vascular in combination with poorly deformable microcytic blood cells. This flow pattern may result in chronic thrombosis of the intrahepatic sinusoids and perpetuate the ischemic injury (Lui et al. 2017).

ACHD patients that were exposed to blood transfusions prior to the ability to screen blood for hepatitis C in 1992 have had a significant (8.6%) risk of contracting this blood-born infection. Chronic hepatitis C therefore remains an important cause of chronic liver disease in the ACHD population and is estimated to affect approximately 5% of the patients. Other conditions that may contribute to liver disease among the ACHD population include hepatotoxic medications such as amiodarone and bosentan which are frequently needed to manage arrhythmias and pulmonary hypertension in the CHD population. Chronic transfusions can cause iron overload syndrome which leads to cirrhosis. Monitoring of patients at increased risk of liver disease is exceedingly important in the CHD population and risk stratification and recommendations for monitoring are now part of the standard of care guidelines for patients with CHD.

Management of Liver Disease in CHD

Early detection is the most important strategy in the care of liver disease associated with CHD. Asymptomatic and subclinical disease are common, and the importance of surveillance and early detection is essential. After a careful physical exam and history, laboratory assessment is recommended. Lab values are frequently abnormal in CHD patients, especially Fontan physiology patients. However, the abnormalities in laboratory values tend to mild in most cases until the hepatic dysfunction becomes advanced. The transaminases, bilirubin, INR, albumin, and total protein are usually abnormal in patients in CHF with both congestion and hypoxemia. Surveillance labs are recommended to access liver status in patients with clinical hepatic dysfunction and those at high risk for liver impairment, such as those with hepatic congestion and

low cardiac output. Fontan patients are recommended to begin monitoring for liver disease 5 years after their Fontan completion procedure. Recommended laboratory studies for CHD liver monitoring include AST, ALT, GGT, Alk Phos, bilirubin, albumin, total protein, and INR. For patients who received transfusions or underwent heart surgery prior to 1993, it is recommended that hepatitis serologies for hep C and B be obtained.

Hepatic imaging for patients with CHD includes ultrasound, CT, and MRI. Each mode of imaging has its own indications as well as advantages and disadvantages. CT is the most commonly used mode of imaging in advanced liver disease in CHD and carries the risk of further exposure to ionizing radiation. CT findings of irregular liver contour, right hepatic atrophy with hypertrophy of the lateral segment and caudate lobe, heterogeneous enhancement of the liver parenchyma and nodules are indicative of advanced disease (Lui et al. 2017). Hepatic imaging may also show extra hepatic findings such as ascites, splenomegaly, extensive collaterals, and esophageal varices which have diagnostic significance. Indications for imaging besides surveillance of patients at high risk of liver impairment include changes in physical exam, new symptoms, or changes in laboratory findings. The frequency of hepatic imaging is advised at 3–5 years for patients at risk for hepatic disease and 1–3 years for patients with Fontan physiology after 15 years post-Fontan procedure. For patients with advanced liver disease found on imaging studies, it is advised to monitor for hepatocellular carcinoma (HCC) with routine measurements of alpha fetoprotein (AFP) levels. AFP levels in combination with imaging improve the specificity of hepatocellular cancer detection related to CHD. The gold standard for the diagnosis of fibrosis, cirrhosis, and HCC is liver biopsy. The findings histologically of liver disease associated with CHD show sinusoidal dilation and liver fibrosis that coalesces into septa and regenerative nodular areas. The cirrhosis pattern seen in patients with CHD shows bridging of adjacent central veins by fibrotic septation. If a diagnosis of cirrhosis is made, then further work-up including esophagoduodenoscopy is necessary to screen for esophageal varices. Although esophageal varices are reported in patients with CHD, the actual incidence of varices bleeding remains low.

The clinical management of liver disease in patients with CHD is aimed at improving the underlying hemodynamics and decreasing liver congestion and improving cardiac output and minimizing hypoxemia. The presence of cirrhosis and portal hypertension adversely impacts outcomes in surgical interventions and a patient's candidacy for cardiac transplantation. Heart and liver-combined transplantation is now considered the ultimate palliative strategy for patients with failing Fontan physiology and is discussed in this textbook in a separate chapter. Other management strategies include limiting hepatotoxic medications and lifestyle modification to limit alcohol consumption. Infectious etiologies must be treated such as hepatitis C with antiviral therapy. Because of the complex nature of CHD multi-organ dysfunction, it is recommended that the hepatologist caring for the patient be very familiar with CHD-related liver disease.

Pulmonary Disease in CHD

In studies comparing patients with CHD versus healthy controls, it was found that 44% of patients with CHD compared to 9% of healthy patients were found to have diminished pulmonary function due to restrictive lung disease. 89% of patients with Fontan physiology and 76% of patients with repaired Tetralogy of Fallot were found to have restrictive pulmonary disease (Asrani et al. 2012). Forced vital capacity (FVC) and forced expiratory volume in 1 s (FEV_1) have consistently been shown to be reduced in ACHD patients and are indicative of abnormal respiratory mechanics (Lui et al. 2017). Recurrent pneumonia, pulmonary embolus, and pulmonary hemorrhage remain significant complications in the CHD population. Fontan physiology has the added respira-

tory complication of plastic bronchitis. Plastic bronchitis is a complication found in at least 4% of Fontan patients which consists of a lymphatic derangement that leads to bronchial cast formation in the tracheal bronchial system. Pulmonary embolus is a devastating complication that results from the combination of acquired hypercoagulable disease related to renal and liver dysfunction in combination with low cardiac output and stagnate right-sided flow. Pulmonary hemorrhage with hemoptysis is a serious complication of Eisenmenger's syndrome and Tetralogy of Fallot/ pulmonary atresia with many aortopulmonary collaterals (TOF/PA MAPCA) and occurs in approximately 30% of patients with this anatomy. Pulmonary infections/pneumonia is known to be one of the leading causes of death in patients with CHD and is multifactorial in its predilection.

The pathogenesis of pulmonary disease is generally a result of restrictive lung disease caused by intrinsic disease or lung parenchymal disease or extrinsic causes such as chest wall malformations, neuromuscular disease, and pleural disease processes. It is not uncommon for patients with CHD to have both intrinsic and extrinsic processes leading to significant restrictive lung impairment. The extrinsic component of the restrictive physiology is largely related to the chest wall anomalies from multiple sternotomies, pectus excavatum, and thoracotomies (Figs. 5 and 6). Thoracotomies can also result in scoliosis and kyphosis which can contribute to restrictive lung disease and abnormal respiratory mechanics and function. Patients with Fontan physiology and TOF are likely to have undergone multiple palliative chest procedures and are most likely to have impaired chest wall anatomy and a higher incidence of restrictive lung disease. Impaired diaphragmatic function is also a significant source of extrinsic respiratory dysfunction in CHD. Paresis and paralysis of a hemidiaphragm can cause respiratory disease and are very common complications of recurrent heart surgery. Routine chest X-ray is diagnostic for diaphragmatic paralysis with an elevated hemidiaphragm noted. Neuromuscular diseases

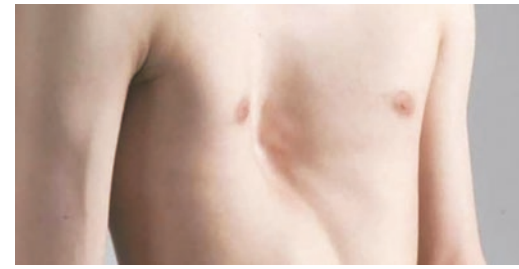


Fig. 5 Sternotomy causing chest wall deformity and pectus excavatum

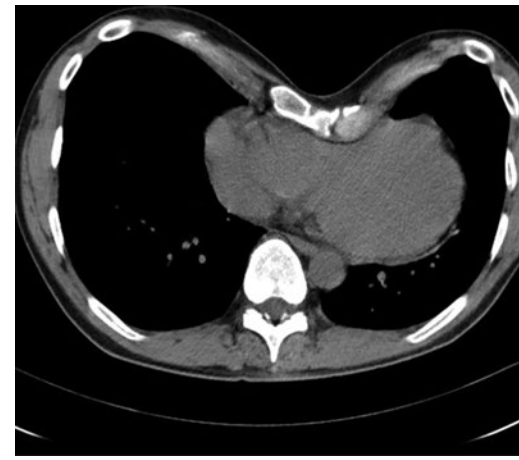


Fig. 6 CT showing chest wall deformity which results in extrinsic restrictive lung disease

such as Duchenne muscular dystrophy, deconditioned states, malnutrition, and chronic heart failure can also result in poor respiratory mechanics due to impaired chest wall strength and respiratory muscle function. Primary causes of intrinsic lung disease include parenchymal disease such as recurrent pneumonia, AVMs, barotrauma, plastic bronchitis, COPD, pulmonary fibrosis, pulmonary hemorrhage, pulmonary hypoplasia, transfusion-related lung injury (TRALI), chronic aspiration syndromes, and pulmonary toxicity from medications such as amiodarone. Pulmonary hypoplasia in the CHD population results from decreased pulmonary blood flow which affects growth of the pulmonary vasculature and parenchyma. This may explain the increased incidence of restrictive lung disease in TOF.

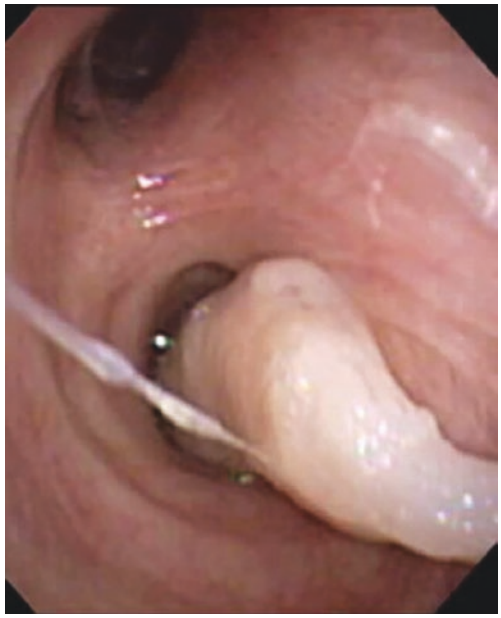
Sedentary lifestyle due to decreased exercise tolerance puts many patients with CHD at risk for obesity. The propensity for obesity can further worsen restrictive lung disease. Obesity worsens chest wall mechanics and is associated with a deconditioned state which is associated with diminished skeletal muscle strength. Obstructive sleep apnea has a known association with obesity and results in intermittent chronic hypoxia, hypoxia-associated pulmonary vasoconstriction, and resulting pulmonary hypertension. As many as 10% of the ACHD population has baseline pulmonary hypertension and the associated pulmonary hypertension of OSA may create adverse hemodynamics in an already tenuous circulation.

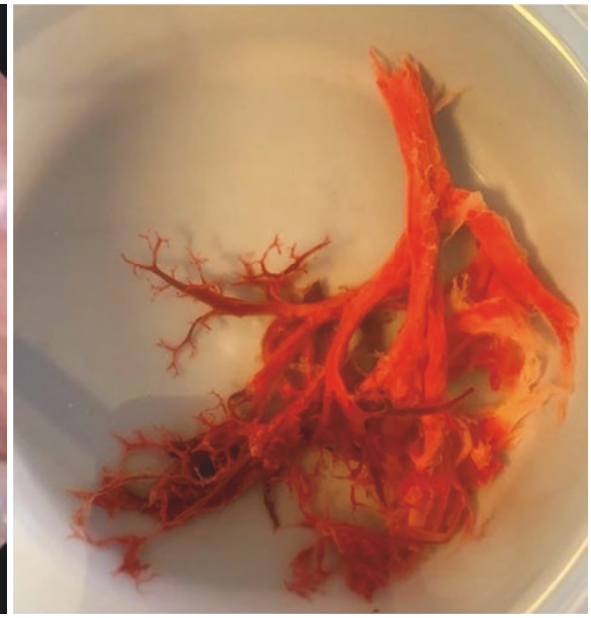
The impact of chronic restrictive lung disease is very common among CHD patients and often under-appreciated. It significantly impacts exercise tolerance and functional capacity. During periods of increased demand, patients will attempt to compensate by increasing their minute ventilation with an increased respiratory rate rather than tidal volume. These patients have increased dead space ventilation, abnormal gas diffusion, decreased vital capacity, decreased lung compliance, and poor respiratory mechanics all contributing to their diminished respiratory reserve. In the setting of restrictive lung physiology, studies of CHD patients have shown significant right heart dysfunction as a consequence of elevated pulmonary arterial pressures due to poor lung and chest wall compliance. This right heart dysfunction is manifested as restricted right ventricular diastolic filling during periods of increased exercise. Left ventricular (LV) dysfunction results from abnormal respiratory mechanics secondary to diminished LV filling and increased afterload. Restrictive lung disease in the CHD population is associated with increased hospitalizations, pneumonia, atrial arrhythmias, and increased mortality (Alonso-Gonzalez et al. 2013).

Management of Restrictive Lung Disease in CHD Patients

The recommendations for screening for restrictive lung disease include obtaining a baseline chest X-ray and formal pulmonary function testing with body plethysmography to confirm the diagnosis by showing the decrease in total lung capacity. The recommended treatment for ACHD patients with moderate to severe restrictive lung disease is pulmonary rehabilitation with endurance training in patients that are able to tolerate this therapy. The studies have predominantly been done in non-CHD patients with restrictive lung disease; however, mounting evidence is encouraging for this population and the benefits outweigh the risks with noted improvement in quality of life and exercise tolerance. Other strategies which are potentially beneficial are weight loss, supplemental oxygen, nighttime use of noninvasive ventilation, respiratory muscle training, and treatment of OSA. Cessation of smoking is part of lifestyle counseling for ACHD patients and is strongly discouraged. The presence of restrictive lung disease and its impact on a patients' individual physiology in the perioperative setting of non-cardiac surgery must always be appreciated with a proper perioperative plan for respiratory support considered.

Plastic bronchitis is a severe complication of Fontan physiology that requires significant medical therapy (Figs. 7 and 8). The current treatment options include sildenafil, steroids, inhaled tissue plasminogen activator, and mucolytics. Procedural treatment options that include lowering central venous pressure and ultimately heart transplant are invasive strategies. Newer percutaneous lymphatic procedures may also offer improvement in cast formation and symptoms. The treatment of hemoptysis in patients with Eisenmenger syndrome and MAPCA anatomy is generally supportive with percutaneous collateral embolization preformed when appropriate.





Figs. 7 and 8 Plastic bronchitis in a Fontan patient

Immunologic Impairment in CHD and Protein-Losing Enteropathy

Immunologic impairment in patients with CHD is primarily a concern in patients with Fontan physiology. The derangement manifests primarily as protein-losing enteropathy (PLE). PLE is the abnormal loss of serum proteins including immunoglobulins in the intestines and occurs in 5–15% of patients with single ventricle physiology (Engelings et al. 2016). The diagnosis requires a high index of suspicion as the patients may initially be asymptomatic. As the conditions worsen, patients may present with hypercoagulable symptoms, ascites, edema, recurrent infection, and hypoalbuminemia. The diagnosis is definitively established by elevated fecal alpha-1 antitrypsin levels. Alpha-1 antitrypsin is an endogenous protein marker for blood proteins not generally present in the intestinal tract. A spot fecal alpha-1 antitrypsin level of >100 mg/mL is indicative of PLE.

PLE is associated with other systemic complications such as hypocalcemia, osteopenia, thromboembolism, infections, and growth insufficiency. PLE causes other immune system perturbations including hypogammaglobulinemia especially IgG_2, and lymphopenia with a selective CD_4 lymphocyte deficiency. Therefore, patients with Fontan physiology have a combined immunodeficiency which results in a similar phenotype like that of severe combined immunodeficiency (SCID) syndrome. Of note, opportunistic infections are rarely reported in these patients. Another immunologic concern for patients with PLE is the fact that vaccinations may not be effective. Despite receiving vaccines, it is frequently found that this group of patients does not have protective antibody titers to childhood vaccines such as the MMR vaccine (measles, mumps, and rubella) as well as hepatitis B. It is thought that due to the loss of immunoglobulins there is a loss of immunity over time.

Although the pathophysiology of PLE is not completely clear, the hemodynamics which are considered to create this physiology are chronic elevated central venous pressures, increased mesenteric vascular resistance, low cardiac output, inflammation with endothelial cell dysfunction, and the loss of intestinal epithelial cell integrity.

The management of PLE is aimed at improving cardiac output and lowering central venous

pressures along with intestinal and pharmacologic strategies. The management aimed at the gastrointestinal tract includes diet management with a low-fat and high protein diet with medium chain triglycerides. This management is aimed at reducing intestinal lymphatic flow and fluid losses. With severe PLE, TPN may be required but carries the added risk of line sepsis and thromboembolism of central venous system. The pharmacological therapies include heparin, steroids, albumin, and immunoglobulin infusions.

The transcatheter techniques are aimed at improving cardiac output and relieving Fontan obstruction, AV valve regurgitation, and decreasing arrhythmia burden. Fenestration of the Fontan may help decrease the Fontan pressure but comes with the added risk of thromboembolism and stroke. Inhaled prostacyclins and Milrinone therapy are also part of the medical regimen.

The ultimate palliative therapy is cardiac transplantation which resolves PLE in the majority of cases (Feldt et al. 1996). Patients with PLE due to Fontan physiology are at increased mortality after heart transplantation. Accordingly, the modern approach to these patients is to intervene with transplantation before PLE has become a complication (Chen et al. 2004).

Infectious Disease Concerns in CHD

Complications related to infectious disease are experienced at a much higher rate in patients with CHD and with significant morbidity and mortality. The propensity for severe infectious complications is related to the abnormal cardiac anatomy and circulation, altered hemodynamics, foreign implanted material, and relative immunosuppression in some cases (Doumouras et al. 2016). The risk of infectious complications is a life-long concern. Patients with small unrepaired VSD shunts are reported to have a risk for endocarditis which is greater than 30 times the risk of the general population (Lui et al. 2017). Patients with cyanotic CHD are at the highest risk of infectious morbidity especially for endocarditis, brain abscesses, and pneumonia. For all procedures in which bacteremia is a risk factor, compliance with antibiotic prophylaxis is imperative. The recommendations for bacterial endocarditis prophylaxis for various cardiac lesions can be found on the American Heart Associations' website and are updated as needed. CHD patients with heterotaxy anatomy are also at significant risk for sepsis from encapsulated bacteria due to their relative asplenic state. Greater than 25% of heterotaxy patients will have had at least one significant episode of sepsis by adulthood. Heterotaxy patients also have primary pulmonary cilia dysfunction which makes them also extremely susceptible to respiratory infections. The encapsulated bacteria which present the greatest risk to CHD patients include: *Haemophiles influenzae, Streptococcus pneumoniae, Group B Streptococcus, N meningitidis, Salmonella typhi, klebsiella pneumoniae,* and *E. coli* (Berglund et al. 2016). For infants, *E coli* and *Klebsiella* are the primary pathogens responsible for sepsis and for patients greater than 6 months, *Haemophiles influenzae* is the most concerning infectious agent. Vaccinations for *H influenz*a is impacting the infectious risk and it is a recommended vaccine for the pediatric CHD population. The risk of death from sepsis among the heterotaxy group is generally greater than 50%.

With the increase in percutaneous transcatheter valve replacements among the CHD population, there has been a significant rise in endocarditis related to the transcatheter pulmonary valve replacement (TCPVR) procedure (Fig. 9). This group is largely made up of patients with RVOT pathology such as TOF and patients with stenotic RV to PA conduits. Staphylococcus aureus is the most common cause of endocarditis in the CHD population regardless of age and is the most common among patients receiving TCPVR (Chiu et al. 2014) (Fig. 10).

Other implanted intra and extra cardiac devices and graft materials are a significant source of infection leading to endocarditis. Pacemakers, ICDs, dialysis catheters, central lines, ports, stents, and vascular grafts are the most common implanted material in the CHD population and must be considered if concerns regarding infectious symptoms are present. Transesophageal echocardiography, CT, MRI, and positron emis-

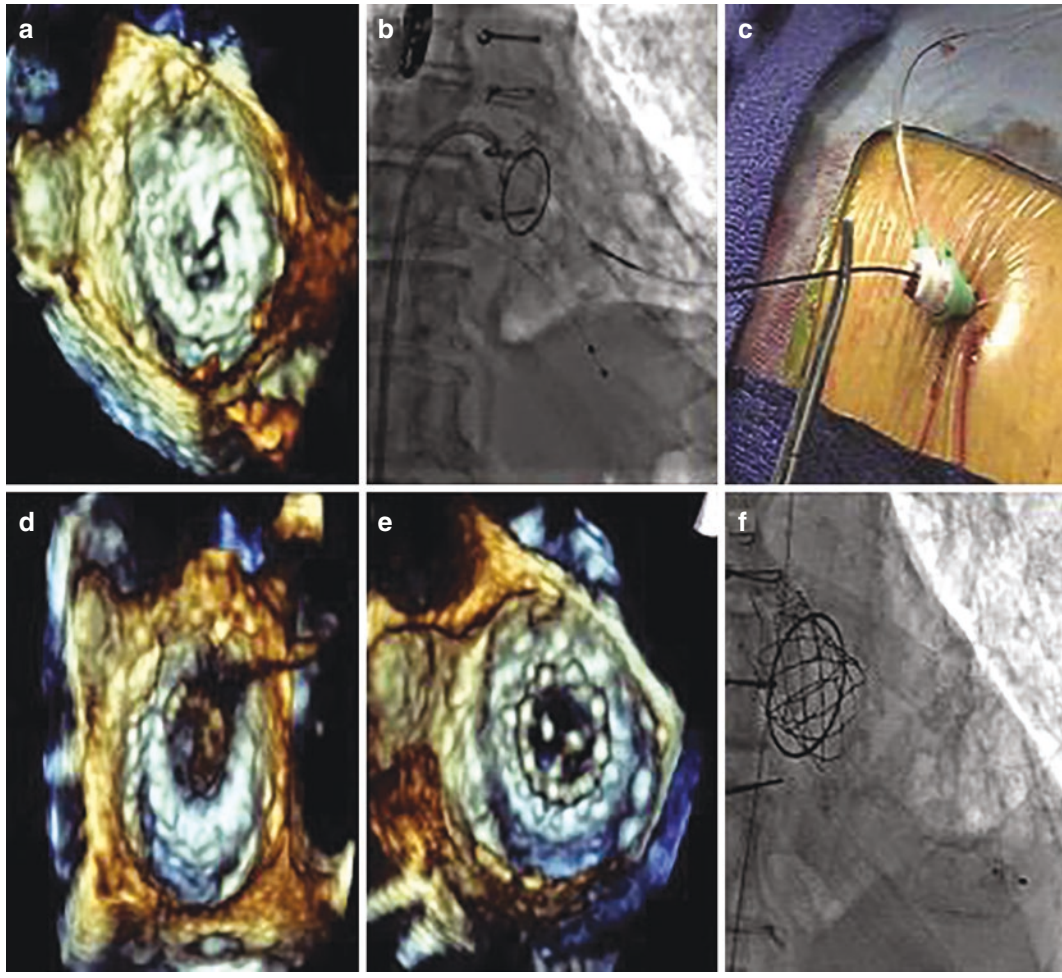


Fig. 9 3D echo of melody valve in pulmonary position with vegetations

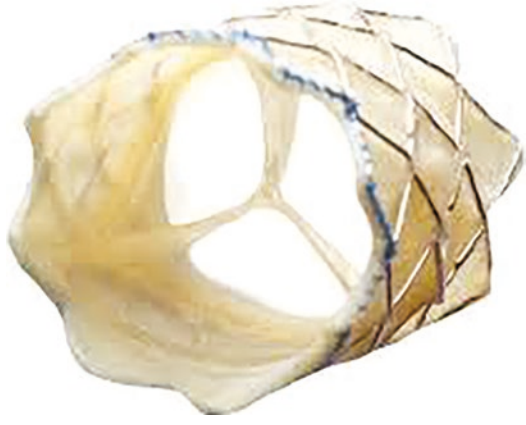


Fig. 10 Transcatheter melody valve medronic.com

sion tomography (PET) scanning are the primary modes of diagnostic imaging.

The most common cause of non-cardiac death in the ACHD population is pneumonia. Death from a respiratory infection is likely due to baseline restrictive lung disease, associated genetic disorders, relative immunocompromise, and congenital abnormalities of the respiratory system. Another reportedly common source of infection among ACHD patients is peritonitis. Liver dysfunction, PLE and renal dysfunction with proteinuria may produce ascites. The resulting ascites can become a site for bacterial infection with peritonitis as a source of severe systemic infection.

If bacterial infection is suspected in CHD patients, it is recommended that pretreatment sputum and blood cultures be obtained. Empiric antibiotic treatment is not recommended. CHD patients with heterotaxy who are 5 years old or younger should receive asplenia prophylaxis and if fever or chills develop, these patients should seek immediate medical attention. Asplenic adults are not given daily prophylactic antibiotics unless they have a history of severe pneumococcal sepsis, HIV, immunoglobulin deficiency, advanced liver disease, or immunosuppression due to transplantation. Heterotaxy patients should be vaccinated against *H influenzae, N meningitidis,* and *S pneumoniae*. All ACHD patients should receive a yearly flu shot and every 5-year pneumococcal vaccine. The current antibiotic recommendations for initial treatment of pneumonia are fluoroquinolone therapy or combination macrolide and beta lactam. Directed therapy is preferred if culture sensitivities are available.

Hematologic Derangements in CHD

There are multiple pathologic hematology abnormalities and derangements in both pediatric and adult CHD patients. Anemia is a common problem for patients in CHF. For patients with cyanotic CHD, erythrocytosis with resulting polycythemia and microcytic anemia creates both hemorrhagic complications and poor release of oxygen to tissues from poorly deformable microcytes and tissue hypoxia. Patients with Fontan physiology suffer from significant venous hypertension, liver and renal dysfunction which results in thrombosis in areas of stagnant blood flow due to a hypercoagulable state and bleeding from lack of clotting factor production, protein-loss, and high collateral burden.

Secondary erythrocytosis is a compensatory mechanism that results from low oxygen tension and the body's adaptive response to produce more red cells. Unfortunately, the cells are iron-deficient, small, microcytes that are not properly deformable in the circulation and cannot bind or release oxygen to the tissues due to the lack of functional hemoglobin. The tissue hypoxia is worsened by the increased blood viscosity due to polycythemia and poor flow dynamics due to the pathologic red cell shape. Patients with profound cyanosis such as Eisenmenger syndrome patients suffer from hyperviscosity syndrome and are prone to strokes, thrombotic complications, bleeding complications, end-organ hypoxia, myalgias, pathologic hip fractures due to femoral head necrosis, headaches, seizures, visual impairment, chest pain, and vertigo (Van Dijck et al. 2015). There is no specific hematocrit at which hyperviscosity syndrome occurs. Patients with cyanotic CHD are followed with routine complete blood count (CBC) and iron studies. Patients who present with symptoms of hyperviscosity are acutely treated with hydration. If neurologic symptoms are present, brain imaging may be indicated. Treatment with prophylactic phlebotomy to prevent hyperviscosity symptoms is not recommended because it precipitates iron deficiency, lowers oxygen carrying-capacity, diminishes exercise tolerance, and increases the risk of stroke (Collins et al. 2008). There are currently only two clinical indications for therapeutic phlebotomy in this setting: severe refractory symptomatic hyperviscosity and preoperative autologous blood donation.

The diagnosis and treatment of iron deficiency in cyanotic CHD requires surveillance iron studies including iron levels, ferritin, and transferrin saturation. Iron deficiency is treated to improve oxygen-carrying capacity, exercise tolerance, and diminish symptoms of anemia such as headache, fatigue, and restless leg syndrome. The concern of worsening erythrocytosis does not diminish the need for iron repletion. Studies have not indicated worsened symptomatic hyperviscosity and have shown an improvement in functional class and no baseline hematocrit is considered too high for iron repletion. Either oral or IV iron is effective. Oral therapy is easily achieved and available but does have the side effect of nausea and constipation. IV iron is more effective but can precipitate anaphylaxis (Broberg 2016).

Thrombotic and Hemostatic Considerations in CHD

The types of thrombotic complications are similar among CHD and ACHD patients with CHD. However, adult patients have a heavier arrhythmia burden, increased risk of stasis with collaterals, residual shunts and hemodynamic anomalies which place them at significant risk for thromboembolic events (Lui et al. 2017). The incidence of strokes and other thromboembolic events is significantly higher in the ACHD population compared to the age-matched general population. Clinical thrombosis occurs in up to 33% of Fontan patients and asymptomatic thrombosis exists in significantly more patients (Tay et al. 2011). Asymptomatic thrombi can be found in the venous connections, pulmonary arteries, Fontan conduits (Fig. 11), and atrial connections. Arrhythmias significantly increase the risk and existence of subclinical thrombosis and intracardiac clot formation.

Patients with Eisenmenger's syndrome have a propensity for both thrombotic and hemorrhagic complications (Lanz et al. 2015). The hemorrhagic complications are largely related to both a qualitative and quantitative defects in platelets. Cyanotic patients have a baseline thrombocytopenia which results from ineffective thrombopoiesis and impaired platelet survival. Platelet dysfunction also results for ineffective ADP-induced platelet aggregation. The PTT, PT, and INR are frequently abnormal due to congestive hepatopathy-induced liver dysfunction and diminished production of vitamin K-dependent coagulation factors and depletion of Von Willebrand's factor. Epistaxis is a frequent presenting symptom of the coagulopathy that is present in Eisenmenger's patients. These patients have a contracted plasma volume and elevated hematocrit which interferes with falsely prolonged PT and a PTT due to the abnormal ratio of plasma to citrate anticoagulant.

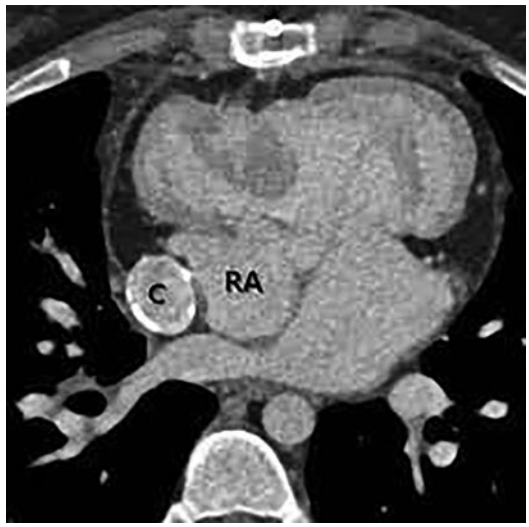


Fig. 11 CT showing thrombus in Fontan conduit (C)

The most common coagulation abnormalities in Fontan physiology patients are diminished protein C levels and factor VII deficiency. Other abnormalities include diminished fibrinolysis, platelet activation, and thrombin formation which all create a prothrombotic state. The most useful imaging modalities include TEE, CT, and MRI depending on the site of suspected thrombosis.

Management of Coagulation Abnormalities

The management of anticoagulation in patients with cyanotic congenital heart disease, especially Fontan and Eisenmenger physiology patients, remains a dilemma due to the potential for simultaneous thrombotic and life-threatening bleeding complications (Perloff et al. 2003). In the care of Eisenmenger patients, studies have not shown survival benefit while the risk of significant bleeding complications has been as high as 16% in patients who received therapeutic anticoagulation. Routine anticoagulation for Eisenmenger syndrome has not been recommended in the American or European guidelines, although acute or chronic thrombotic complications may warrant treatment.

Fontan patients have an extremely high rate of thrombotic complications over their lifetime. In this patient population, thromboprophylaxis is recommended. It is not clear if anti-platelet ther-

apy alone is sufficient or if therapeutic anticoagulation is warranted in patients without previous thrombotic complications or arrhythmias. Currently, most patients receive aspirin anti-platelet prophylaxis. Studies have not shown that therapeutic anticoagulation with warfarin has a benefit over aspirin anti-platelet therapy. Multi-center trials are ongoing and will hopefully be available for future guidelines soon.

Endocrine Abnormalities in CHD

Multiple syndromes that involve CHD also have concomitant congenital endocrine disease. Examples of this include Turner and Down syndromes which frequently have associated hypothyroidism, diabetes mellitus, osteopenia, and hyperlipidemia. DiGeorge syndrome has associated hypoparathyroidism and thyroid disease along with multiple forms of CHD. William's syndrome is known to have associated hypercalcemia, hypothyroidism, and diabetes in addition to significant aortic, pulmonic, coronary and renal artery stenosis. Endocrine disease in CHD is not unique to patients with genetic syndromes. Patients with Fontan physiology and congestive heart failure are often Vitamin D-deficient with hyperparathyroidism and have osteoporosis (Potter et al. 2013). Age-related acquired adult endocrine disease is common in patients with CHD. Obesity, metabolic syndrome, diabetes mellitus, and hyperlipidemia are very common among the ACHD population and impact acquired cardiovascular disease with increased risk of atherosclerotic heart disease and peripheral vascular disease. Recognition of associated endocrinopathies and acquired endocrine disease in this population is part of the multi-system approach. Diagnosis and management of these abnormalities is vital to the overall health and longevity of a patient with CHD. These endocrine abnormalities can also impact the perioperative management and outcomes of patients with CHD and consultation with endocrinology practitioners who are familiar with endocrine disease related to CHD and genetic syndromes are vital.

Thyroid Disease in CHD

The most common endocrine pathology is thyroid disease. Hypothyroidism is found in approximately 10% of the ACHD population. It is found in most cyanotic patients, Down syndrome, and as a result of amiodarone treatment. Hypothyroidism affects nearly 20% of Down syndrome patients and may be related to autoimmune disease. The incidence of hypothyroidism in Turner syndrome is nearly 30%. For patients receiving amiodarone with CHD, the incidence of hypothyroidism is approximately 20%. Amiodarone-induced hypothyroidism in the non-CHD patient population is between 2–and 10%. CHD patients with female gender, low BMI, Fontan physiology, cyanotic heart disease, Eisenmenger syndrome, goiter, and heart failure are at increased risk of developing amiodarone hypothyroidism. Prostacyclin treatment for pulmonary hypertension has also been linked to hyperthyroidism and thyrotoxicosis. Screening is recommended in all CHD patients with risk factors. Testing thyroid-stimulating hormone (TSH) and free thyroxine is recommended every 6 months in patients receiving amiodarone. The management of hypothyroidism in CHD patients is not different from the management in the general population. However, due to the concern for atrial arrhythmias, care must be taken with an increase in dosage. The diagnosis and treatment of thyroid disease in CHD patients is important due to the risk of poor outcomes and perioperative morbidity in untreated patients. Thyrotoxicosis treatment in patients receiving amiodarone is similar as in patients without CHD.

Calcium Metabolism and Bone Disorders in CHD

Endocrine disorders related to vitamin D and calcium metabolism are found in multiple genetic syndromes and are also a result of cyanotic CHD and chronic cardiac failure. Disorders of calcium metabolism can result in arrhythmias as well as disorders of the bone and pathologic fractures.

Elevated parathyroid hormone levels and low vitamin D levels are associated with CHD. Patients with advance heart failure have also been found to have lower bone density and vitamin D levels resulting in osteopenia and osteoporosis (Martínez-Quintana et al. 2013). Patients with Down syndrome have decreased bone density and pathologic fractures. Turner syndrome patients have osteoporosis related to the concomitant estrogen deficiency and 80% of DiGeorge patients are hypoparathyroid and require calcium supplementation to avoid tetany, seizures, and arrhythmias. Non-syndromic patients, which are at risk for defects in calcium homeostasis, include Fontan patients and those with cyanotic CHD. Fontan patients, especially those with PLE who are treated with corticosteroids, are at the highest risk. Fontan and single ventricle physiology patients have diminished bone density starting in childhood. The etiology of diminished bone density in Fontan patients is likely multifactorial and due to hypoxemia, decrease weight bearing activity, reduced sun exposure, corticosteroids, malabsorption, chronic liver disease and reduced serum protein and albumin levels. Patients that have pathologic fractures or known risk factors should be screened for abnormal calcium metabolism with bone density evaluation, calcium levels, parathyroid levels, and vitamin D levels (Lui et al. 2017). The management includes calcium and vitamin D supplementation with weight bearing exercise.

Diabetes in the CHD Population

Approximately, 40% of the ACHD population has impaired glucose tolerance compared to 9% of the age-matched general population. Syndromic ACHD patients with Down, Turner, and William's syndrome have a significant lifetime risk of developing DM. The causes of this increased risk of DM are likely multi-factorial and related to increased rates of obesity, metabolic syndrome, and decreased exercise tolerance among this patient population. The impact of DM in the CHD group is related to increased cardiovascular morbidity. The recommendations for screening the CHD population are to begin at ≥40 years of age with a BMI ≥25 kg/m^2 with or without risk factors. Fasting glucose levels, oral glucose tolerance, and hemoglobin A1C are the standard laboratory assessments. In the case of cyanotic CHD and erythrocytosis, the interpretation of the hemoglobin A1C may be difficult. In this case, the fructosamine level may be more useful.

Obesity, Metabolic Syndrome, and Hyperlipidemia in CHD Patients

The prevalence of obesity among patients with ACHD is approximately 40–54% which is similar to rates in the general population. However, there is increased morbidity and mortality associated with obesity and metabolic syndrome when superimposed on the hemodynamics and sequelae of CHD. Thirty percent of redo sternotomy patients with CHD have documented obesity and this impacts recovery and perioperative morbidity. Fontan patients are a subgroup of CHD patients with increased risk of obesity at approximately 30–40% (Pemberton et al. 2010). Metabolic syndrome occurs at twice the rate of the general population in CHD patients with 15% of CHD patients having hypertriglyceridemia and elevated fasting hyperglycemia.

The causes of metabolic syndrome and obesity are multifactorial in this group. CHD patients generally have decreased exercise tolerance and are more prone to a sedentary lifestyle. Deconditioning due to intrinsic physical limitations is imposed on patients and may be difficult to overcome. Multiple procedures and recovery times, risks of anticoagulants are other concerns related to exercise described by CHD patients. Abnormal growth patterns and increased rapid weight gain after palliation in pediatric CHD patients frequently appear to set the stage for obesity in young patients (Shane et al. 1997).

Perioperative complications such as arrhythmias, respiratory impairment, and longer postoperative stays have been documented in patients with CHD and obesity. The effects of increased

afterload and extrinsic restrictive lung disease on ventricular function are significant, especially for patients with single ventricular physiology. Patients with Fontan physiology have a direct correlation between obesity, heart failure, and accelerated liver disease.

The management of obesity and metabolic syndrome include yearly weight assessment, BMI, and counseling with a comprehensive discussion and referral to nutritionist if necessary. Bariatric surgery is another option for patients with a BMI $\geq$40 kg/m^2 or lower BMI if obesity-related comorbidities are present. Exercise recommendations and lifestyle modification, as well as the treatment of hypertension, dyslipidemia, and cessation of smoking are all part of the management.

The rates and treatment of dyslipidemia are similar in prevalence to the general population and treated in a similar manner. Certain lesions such as coarctation of the aorta and patients who are status-post arterial switch are more vulnerable to cardiovascular atherosclerotic risks and require increased vigilance and early intervention. The only ACHD group in which conventional therapy has been studied has been normotensive patients who have undergone childhood coarctation repair. These patients were treated with atorvastatin and ramipril and were shown to have lower vascular inflammatory markers which are known to be abnormal and elevated in this group of patients.

Vascular and Cerebrovascular Disease in CHD

Vascular and cerebrovascular diseases in CHD are a diverse collection of disease processes which consist of both congenital and acquired vascular disorders. The venous and arterial systems are involved along with both systemic and pulmonary circulations. The pathologic processes include anatomic malformations, genetic syndromes, previous cardiac and interventional cardiology procedures, atherosclerotic disease and physiologic compensatory mechanisms and sequelae.

Cerebrovascular disease including strokes and transient ischemic attacks (TIA) is a prevalent complication of ACHD. Males with CHD have a 1 in 11 risk of stroke and females have a 1 in 15 risk of stroke between the ages of 18 and 64 years of age (Freud et al. 2015). The incidence of stroke in the CHD population is much higher than the general population and may occur at a younger age. Ischemic strokes are more common than hemorrhagic strokes and the risk is higher if congestive heart failure, DM, or a recent MI has occurred. The etiology of cerebrovascular disease in CHD patients is associated with abnormalities in coagulation and vascular arteriopathy such as single ventricle physiology with a hypercoagulable state, stagnate blood flow, and right to left shunting. Other contributing factors to embolic strokes in CHD patients include mechanical valves, right to left shunts, atrial arrhythmias, depressed ventricular function, and conduits or vascular segments with stagnate blood flow.

Atrial arrhythmias are a common sequela of CHD and place patients at extremely high risk for thromboembolic strokes. Patients with atriopulmonary Fontan anatomy with atrial arrhythmias have significant risk of embolic stroke due to intracardiac thrombi which are present in approximately 75% of this group of patients. Monitoring and treatment of dysrhythmias is critical. Anticoagulation is part of the management algorithm and should be given when right to left shunts exist as is the case with Fontan fenestrations and Ebstein's anomaly with severe tricuspid regurgitation and ASD. Cerebrovascular imaging with MRI or CT is utilized if suspicion of embolic stroke is present and should be part of the evaluation in collaboration with neurology.

Hemorrhagic stroke and subarachnoid hemorrhage as a result of ruptured intracranial aneurysm is a rare complication in the CHD population and is a known risk factor for patient with coarctation of the aorta (CoA). There is a known association between CoA and intracranial aneurysms which is thought to be due to arteriopathy/aortopathy. The arteriopathy and concomitant hypertension associated with CoA are the pathophysiologic factors which can result in aneurysm formation and rupture.

Peripheral Venous Disease

Venous hypertension and insufficiency are a frequent complication of elevated right-sided cardiac pressure states in CHD. Fontan and other single ventricle patients on anti-arrhythmic and with a family history of venous insufficiency are at the highest risk for developing venous insufficiency. Previous central line placements and cath procedures may also cause venous disease and obstruction. Hypercoagulable states are common in CHD especially Fontan and other single ventricle states and may place patients at risk for DVT and PE. In patients with an interrupted IVC there is an increased incidence of incidence of DVT which implies heterotaxy with polysplenia patients must be monitored for potential DVT formation due to IVC abnormalities. Venous obstruction due to multiple procedures and central line placement can also result in stagnate venous flow and result in thrombus formation in the venous circulation. In the assessment of venous insufficiency, ultrasound of the lower extremities is the diagnostic entity of choice. CT angiogram to evaluate for PE can be difficult to interpret in ACHD patients with abnormal pulmonary blood flow. There is also a propensity to develop collateral circulation. Ankle-brachial index is a useful assessment to evaluate for decreased lower extremity blood flow in patients with coarctation who may be asymptomatic.

Aortopathy and Arteriopathy in CHD

Aortic root dilatation occurs as a result of anatomical CHD and congenital connective tissue disorders such as Marfan's disease, Ehlers-Danlos, Turner syndrome, and Loeys–Dietz syndrome. TOF and other conotruncal abnormalities such as double-outlet right ventricle and truncus arteriosus also have a predisposition for aortic root dilatation and aortopathy. Aortic dissection is a late complication after TOF, arterial switch, Ross, Norwood, and coarctation repairs. In repairs in which the pulmonary artery is used as the neo-aorta there is a compensatory dilatation of the vessel in response to left heart pressure and shear-force. Aortic insufficiency without stenosis may also develop due to the dilatation. Endothelial dysfunction is a known risk for patients with coarctation of the aorta and persists after successful repair (Abiodun et al. 2016). It manifests as focal, decreased aortic compliance, and increased left ventricular mass and hypertension. Fontan patients are also at risk for arteriopathy and endothelial dysfunction. The lack of pulsatility in the pulmonary vascular bed impairs the vasorelaxation response which is endothelium dependent. This impaired endothelium function may increase pulmonary vascular resistance and result in the physiologic changes seen after Fontan palliation. For CHD patients with risk factors for aortic dilatation, it is recommended that patients have surveillance imaging at a CHD center. Echocardiography is the first line imaging modality with CT and MRI used if advanced imaging is required. Patients with a history of coarctation should be followed with aortic imaging at least every 5 years.

Hypertension in the CHD Population

The incidence of hypertension is increased in the CHD population. The highest risk patients include those with combined renal and cardiac anomalies, coarctation and cyanotic heart disease. Patients with coarctation status post repair without a residual gradient may have hypertension despite the presence of a gradient (Cordina et al. 2015). Approximately, 60% of patients with repaired coarctation have chronic hypertension. Hypertension in the CHD population is associated with obesity, diabetes, dyslipidemia, sleep apnea, and increased inflammatory markers (Lui et al. 2017). The management of hypertension is similar to that of the general population. The diagnostic work-up includes evaluation of end-organ dysfunction including urinalysis, blood glucose levels, hematocrit, basic metabolic panel,

and lipid panel. Patients should be screened for known causes of hypertension such as non-steroidal anti-inflammatory drugs, endocrine disease, renovascular disease, and obesity. The medical management is aimed at afterload reduction and prevention of abnormal ventricular remodeling. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in combination with mineralocorticoid receptor blockers may be cardioprotective.

Oncologic Complications in CHD

Malignancy is the fourth leading cause of death in the ACHD population after cardiac failure, pneumonia, and sudden cardiac death. Patients over 65 years of age with CHD are twice as likely to die from cancer compared to the general population according to a Canadian registry. The pathogenesis is due to the increasing use of ionizing radiation from imagining diagnostic studies and catheterization laboratory procedures. The number of radiation exposures has increased significantly over the years and the age of initial exposure has declined to younger patients (Hager et al. 2007). These procedures have been deemed standard of care and will require greater vigilance in the number of exposures required in the future to minimize the oncologic risk. Genetic abnormalities are another risk factor for malignancy. Down syndrome, Noonan syndrome, Fanconi anemia, and 22q11.2 defect are associated with the development of malignancy. The deletion of 22q11.2 is associated with conotruncal malformations and may also play a part in the development of malignancy. Down syndrome is a known risk factor for both congenital heart disease and leukemia and lymphoma. Fanconi anemia is an autosomal, x-linked recessive disease with bone marrow failure, leukemia, and solid tumors along with CHD in the form of VSD, coarctation, PDA, truncus arteriosus, pulmonic stenosis, and aortic stenosis (Lui et al. 2017). Teratogenic insults with a link to CHD and cancer may also share an origin.

The initial age of exposure has been shown to be a critical determinant of malignancy development. The ACHD population has frequently been exposed to significant radiation in childhood due to cardiac catheterization procedures which were the primary mode of CHD diagnosis. Echocardiography did not become a proven diagnostic modality in CHD until the 1980s.Children exposed to radiation have increased risk of malignancy due to rapid cell division, significant radiation scatter, and longer life expectancy. Cardiac catheterization, CT scans, and repetitive postoperative chest x-rays are the predominate radiation exposure risks for pediatric cardiology and cardiac surgery patients. There is no threshold below which radiation does not cause malignancy. Low-dose radiation has been shown to cause malignancies in a linear dose-dependent fashion. CHD patients with the highest exposure risk are those with concomitant syndromes and complex cyanotic heart disease (Lui et al. 2017).

Solid malignancies caused by radiation exposure tend to occur at the ages in which they are found in the general population and to be of the same type. Radiation-induced leukemia tends to occur approximately 3–5 years after the exposure. The most frequently found malignancies in the CHD population are the same as the age-matched general population and include thyroid, colon, breast, uterine, prostate, and bladder cancers. The pediatric CHD population is more sensitive to bone marrow malignancies, thyroid, brain, breast, and skin cancers. Fontan patients are at risk for hepatocellular carcinoma (HCC) and the potential contribution for low dose ionizing radiation in the development of this cancer is unknown. Guideline-based surveillance for HCC in patients with FALD is generally done with ultrasound-guided imaging with MRI and CT used in patients in which more detailed imaging is required. The management of HCC in FALD patients may include percutaneous liver ablation, trans-arterial chemoembolization, surgical resection, and combined heart–liver transplantation in the case of failed Fontan physiology with HCC (Harbron et al. 2017).

Mental Health, Well-Being, and Social Impact of CHD

Both children and adults with CHD are at high risk for mental health challenges, neurocognitive impairment, and social challenges. Approximately, 30% of ACHD patients have anxiety and depression disorders and 20% report symptoms of post-traumatic stress disorder (PTSD) (Lui et al. 2017). Children with CHD are at very high risk of neurodevelopmental deficits which correlate in severity with the complexity of their cardiac disease (Ghaferi and Hutchins 2005). These deficits include hypoxic ischemic encephalopathy, developmental delay, speech and language deficits, attention deficit, and hyperactivity and increased risk for special services requirements.

The psychologic and social effects of living with a severe multi-systemic disease must be appreciated when considering the life-long care of these patients. Recurrent painful procedures which leave permanent scars and mental trauma lead to a collective trauma over a patients' lifetime that should not be underestimated. Patients with CHD report body-image concerns, difficulty with social interactions, isolation, and fear of expectation. Parental over-protection is a common anxiety issue reported by ACHD patients. This cumulative experience has been linked to low mood and chronic anxiety issues in ACHD patients. Patients with ACHD have the same goals as their peers with respect to higher education, employment, independent living, family life, and the attainment of good quality of life. However, as a group they tend to have higher rates of unemployment and lower attainment of higher education. The physical scars left from multiple surgical procedures and signs of cardiac pathology such as AICDs create significant body image issues and anxiety which lead to difficult interpersonal relationships (Pagé et al. 2012). All of these concerns impact overall mental health and social well-being.

As CHD patients transition from pediatric cardiac care and medical surveillance, they must start learning to make medical decisions for themselves after many years of parental overprotection. Another significant source of anxiety is the transition from pediatric care providers to ACHD providers. The importance of a health system which provides comprehensive care for CHD patients has been shown to have significant value and improve compliance among this group of patients, while facilitating a smooth transition among care providers (Moons et al. 2005). The importance of offering mental health evaluations and care to CHD patients is vital. Comprehensive regional programs offer this support and have the necessary resources in place. Referral to a regional ACHD center is a vital component to the care of these patients and affects the multi-systemic approach to their care as well as overall well-being and mental health.

Although psychotherapy is the preferred mode of treatment among ACHD patients, pharmacotherapy is another beneficial treatment. Selective serotonin reuptake inhibitors are the safest in treating depression in adults with hemodynamically significant cardiac disease compared to other anti-depressant medications. The most important intervention in the management of mental health issues in the CHD and ACHD populations is the implementation of screening, surveillance, and management of neurocognitive and neurodevelopmental disorders with a comprehensive assessment and treatment team.

Summary

The past three decades have seen great improvements in the lifespan and quality of life for patients with congenital heart disease. The median age of ACHD patients has increased to 40 years of age with the number of patients over 65 years of age increasing dramatically. The incidence of extra-cardiac comorbidities as a result or sequelae of CHD greatly impacts the health, lifespan, and quality of life of patients with CHD. These multi-systemic non-cardiac comorbidities contribute significantly to the morbidity

and mortality of CHD patients and must be managed in conjunction with the cardiac hemodynamic consequences. Comprehensive care in a regional center specializing in the care of CHD and ACHD patients is recommended, in order to optimize the multidisciplinary care of these patients and minimize the lifetime trauma of chronic disease.

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Anesthetic Management of Adults with Congenital Heart Disease

Lorraine N. Lubin and Robert Wong

Abstract

Congenital heart defects constitute the most common type of birth defects and occur in approximately 8 in 1000 live births. With the exclusion of bicuspid aortic valve disease, the majority of untreated patients born with congenital heart disease (CHD) expire in childhood with approximately 15–25% surviving into adulthood. Significant advances in prenatal diagnosis, interventional cardiology techniques, congenital heart surgery, anesthesiology, and critical care have allowed approximately 90% of these patients to survive into adulthood. The profile of patients with congenital heart disease has evolved, and now there are estimates to suggest that in the United States, there are more adults than children living with congenital heart disease. Most of these patients will require additional interventional cardiology or cardiac surgical procedures either palliative or curative during adulthood. Although major studies evaluating this population have not been done, adults with CHD are a medically fragile group, which have an increased risk for perioperative morbidity and mortality. Formal guidelines which direct the management of these patients have not been developed; however, the American College of Cardiology recommends that adult patients with moderate to severe CHD be referred to a center specializing in the care of these patients and receive expert consultation with the appropriate care providers such as adult congenital heart cardiologists, surgeons, and anesthesiologists prior to undergoing procedures.

Keywords

Congenital heart disease · Right ventricle
Patent ductus arteriosus · Ventricular septal defect · Bicuspid aortic valve

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Congenital heart defects constitute the most common type of birth defects and occur in approximately 8 in 1000 live births. With the exclusion of bicuspid aortic valve disease, the majority of untreated patients born with congenital heart disease (CHD) expire in childhood with approximately 15–25% surviving into adulthood. Significant advances in prenatal diagnosis, inter-

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ventional cardiology techniques, congenital heart surgery, anesthesiology, and critical care have allowed approximately 90% of these patients to survive into adulthood Marelli et al. (2007). The profile of patients with congenital heart disease has evolved, and now there are estimates to suggest that in the United States, there are more adults than children living with congenital heart disease. Most of these patients will require additional interventional cardiology or cardiac surgical procedures either palliative or curative during adulthood. Although major studies evaluating this population have not been done, adults with CHD are a medically fragile group, which have an increased risk for perioperative morbidity and mortality. Formal guidelines which direct the management of these patients have not been developed; however, the American College of Cardiology recommends that adult patients with moderate to severe CHD be referred to a center specializing in the care of these patients and receive expert consultation with the appropriate care providers such as adult congenital heart cardiologists, surgeons, and anesthesiologists prior to undergoing procedures.

When caring for adult patients with CHD undergoing procedures requiring anesthesia, it is imperative that the providers appreciate the anatomy and physiology which may be relatively unique to each patient. A team approach is required, and the providers should communicate regarding the risks of the procedure, the procedural techniques anticipated, and the ability or lack thereof to compensate for any hemodynamic or physiologic perturbations such as hypovolemia/hypervolemia, anemia, and hypotension.

Epidemiology of Adult Congenital Heart Disease

Approximately 25% of adult patients with structural heart disease have not undergone repair of their lesion because they were not considered to have hemodynamic compromise worthy of intervention. Other patients may be diagnosed in adulthood when seeking medical attention for another condition such as pregnancy. Another subset of adult patients with unrepaired CHD have incurred severe physiologic perturbations as sequelae of their CHD and are no longer candidates for repair of their structural heart lesions. Of the patients with mild unrepaired CHD, the most common lesions include mild aortic valve stenosis secondary to a bicuspid aortic valve, atrial septal defects, small restrictive ventricular septal defects, mild pulmonary valve stenosis, mitral valve prolapse, and isolated congenitally corrected transposition of the great arteries. The majority of patients evaluated in the outpatient setting have previously undergone surgical or interventional catheter-based procedures. Adults who have undergone repair of what are considered uncomplicated lesions such as atrial septal defects (ASDs) or patent ductus arteriosus (PDA) may be indiscernible from unaffected patients. These same lesions if left unrepaired may result in pulmonary vascular disease/pulmonary hypertension or Eisenmenger syndrome (Baum & Perloff 1993). Patients with pulmonary vascular disease/pulmonary hypertension or Eisenmenger syndrome especially with cyanosis constitute an extremely high-risk population.

Cyanotic heart disease includes structural heart defects that result in a decrease in pulmonary blood flow or result in mixing of oxygenated and deoxygenated blood. These conditions lead to reduced blood oxygen content and cyanosis. The majority of patients with adult cyanotic congenital heart disease will have had previous surgical interventions as children. The most frequently encountered cyanotic defects managed in the adult congenital heart patient population include tetralogy of Fallot, D-transposition, single-ventricle anatomy, truncus arteriosus, total anomalous pulmonary venous return, and double outlet right ventricle (Table 1).

Table 1 Most commonly encountered adult congenital heart lesions

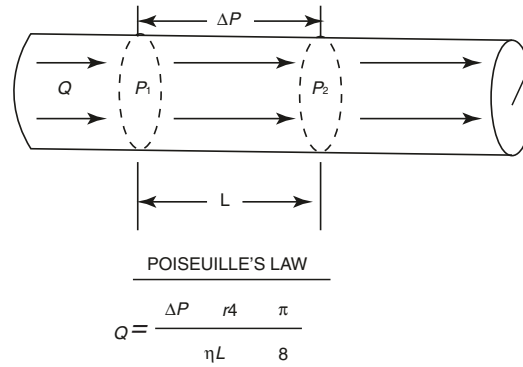
Tetralogy of Fallot, truncus arteriosus, and double outlet right ventricle with conotruncal anomalies postrepair
Secundum atrial septal defect
Ventricular septal defect
Complex single ventricles post-Fontan procedure
Coarctation of the aorta postrepair
Congenital aortic valve stenosis
Atrioventricular canal defects postrepair
Congenitally corrected transposition of the great arteries
Sinus venosus atrial septal defects with partial anomalous pulmonary venous return
Transposition of the great arteries after atrial or arterial switch

Major Categories of Congenital Cardiac Structural Defects

Adult congenital heart disease (ACHD) is composed of a variety of structural anomalies with hemodynamic consequences, which result from both the native anatomy and compensatory physiology. Due to the multitude of structural malformations, including complex forms with combined lesions, a classification system based on physiologic effects is the most useful. *The four categories, which are most commonly used, include shunt lesions, mixing lesions, obstructive lesions, and regurgitant lesions.* Over time, a compensatory physiology will evolve and produce aberrant loading conditions and potential impairment in ventricular function. In some patients, the compensatory changes are imperceptible and may cause little impairment in functions, while other lesions or their combined anatomy may cause significant cardiovascular compromise.

Shunt Lesions

Shunt lesions result in an aberrant communication between cardiac structures. The direction and volume of blood flow depends on the diameter and length of the communication and its relative position in the heart. The shunt lesion can occur at the level of the atria, ventricles, and great vessels or even be extra-cardiac. The flow of blood across the shunt or a vascular structure is determined by a number of factors, including the pressure drop across the structure, length, radius, resistance, and fluid viscosity. Poiseuille's law describes this relationship in the following equation:



where Q = blood flow, ΔP = pressure change in the fluid as it flows across the shunt, r = radius of the structure, L = length of the structure, and \ (n\) = the viscosity of blood. From this equation, it is seen that blood flow increases dramatically with increases in radius, increases to a lesser degree with increase in the pressure gradient across the structure, and decreases with an increase in length of the structure and blood viscosity. With a decrease in radius, a consequential decrease in blood flow to the fourth power is observed. Ohm's law describes the change in pressure, blood flow, and vascular resistance by the following equation:

$$Q = \Delta P / R$$

In this equation, P = the pressure generated within the cardiac chamber, Q = flow, and R = vascular resistance.

The direction and magnitude of shunt defects at the ventricular level and at the level of the great vessels, for example, a PDA, are determined by the radius of the defect and the difference in pulmonary and systemic vasculature resistance. For shunts at the level of the atrium, the ventricular diastolic pressure must also be taken into account. For small shunts, which persist into adulthood,

the indication for repair is based on the potential risk of strokes from paradoxical emboli and the occurrence of bacterial endocarditis. Moderate to large shunt defects can lead to ventricular failure due to volume overload. Shunt lesions that result in chronic increases in pulmonary blood flow may result in Eisenmenger syndrome. Eisenmenger syndrome is an irreversible increase in pulmonary vascular resistance (PVR) that ultimately leads to pulmonary hypertension, right-sided heart failure, and right-to-left shunting. An anesthetic consideration regarding right-to-left shunting is that inhalation inductions may be delayed. However, these delays may be more marked with larger shunts and insoluble anesthetic gases.

Mixing Lesions

Mixing lesions occur when blood from the pulmonary and systemic circulations combines to create a mixture of oxygenated and deoxygenated blood. As with shunt lesions, mixing defects may occur at the level of the atria, ventricles, or great vessels. The ratio of pulmonary and systemic flow is again based on vascular resistance. Increased pulmonary blood flow results with elevated systemic vascular resistance (SVR). This flow pattern results in ventricular volume overload and pulmonary hypertension. Vascular medial hypertrophy of the pulmonary vessels occurs and results in increased PVR and pulmonary hypertension. In severe cases of pulmonary overcirculation, systemic malperfusion occurs with resulting metabolic acidosis, shock, and cardiovascular collapse. Conversely, elevated PVR results in increased systemic flow, decreased pulmonary flow, hypoxemia, and cyanosis. Depending on the underlying anatomy, most patients with mixing defects receive palliation or complete repair in the neonatal period. Patients with ductal-dependent lesions frequently require a mixed circulation before repair. D-Transposition of the great vessels is a defect in which a mixing lesion is required for survival and an atrial septal defect may need to be created by the Rashkind procedure (balloon atrial septostomy) to allow mixing at the atrial level and prevent a circulation in parallel. Depending on the degree of systemic hypoxemia secondary to mixing of saturated and desaturated blood, deficits in oxygen delivery may exist with resulting compensatory mechanisms, including erythrocytosis and polycythemia with resulting hyperviscosity. Patients with mixing lesions are also at risk for bacterial endocarditis and paradoxical emboli and stroke. Other considerations for patients with mixing lesions include the degree of biventricular dysfunction and loading conditions as well as the function of other organ systems Brickner et. al. (2000).

Obstructive Lesions

Obstructive or stenotic lesions impose a ventricular pressure load proximal to the defect that results in increased intracavitary pressure and concentric ventricular hypertrophy. Initially, the wall stress is preserved; however, over time the vascular supply becomes inadequate to support the hypertrophied ventricle. The ventricle becomes relatively ischemic and dilated with increased wall tension and decreased contractility. Chronic obstructive lesions also lead to decreased ventricular compliance and diastolic dysfunction, even in cases with preserved systolic function. Patients with obstructive lesions are extremely preload dependent for adequate diastolic filling and cardiac output. Lesions, which are severely obstructive, can present with inadequate cardiac output and perfusion of the pulmonary, coronary, cerebral, and peripheral tissue beds. Significant decreases in exercise tolerance and cardiovascular reserve may be seen in patients with obstructive lesions.

Regurgitant Lesions

In general, regurgitant lesions do not usually exist as primary defects. They more commonly develop as sequelae or as a result of intervention secondary to CHD. However, worsening valvular incompetence or regurgitation results in decreases in ventricular ejection volume and function. The

compensatory mechanisms to increase stroke volume cause ventricular dilation with increased wall tension and a propensity for ventricular failure. A significant number of interventional cardiac catheter-based procedures and even cardiac surgical interventions are performed to correct lesions such as pulmonary regurgitation after tetralogy of Fallot repair in the adult congenital heart population.

Acyanotic Congenital Heart Disease

Dextrocardia

Dextrocardia is usually described as the heart having a mirror-image location in the right hemithorax. Dextrocardia with situs inversus is a mirror-image location of the intrathoracic structures as well as the intra-abdominal structures. This cardiac anomaly causes the heart to lie in the right hemithorax with the liver and gallbladder under the left portion of the diaphragm. The stomach is located under the right portion of the diaphragm and the appendix is located in the left lower quadrant. Dextrocardia with situs inversus may be functionally normal. Isolated dextrocardia with normally related abdominal viscera frequently indicates the presence of CHD. In some patients, the stomach bubble may be indistinguishable from large bowel gas because the stomach is not in its usual position, either left or right, and the liver appears to be uniformly distributed across the right and left diaphragm. This suggests visceral heterotaxy or situs ambiguous, associated with either polysplenia or asplenia and a high incidence of congenital heart malformations. In these patients, the apex may point to the left, right, or anteriorly and is referred to as mesocardia or atrial isomerism.

Dextrocardia with situs inversus usually exists in otherwise structurally and functionally normal hearts. These patients will generally have their congenital malpositioning noted when they present for noncardiac-related medical attention. The risk of noncardiac surgery in patients with dextrocardia with situs inversus and otherwise structurally normal hearts is the same as for patients with situs solitus (normally positioned abdominal viscera) and normally positioned hearts. The importance of diagnosing this anomaly lies in the correct interpretation of symptoms related to the underlying anatomic location of the organ in question. For example, patients with dextrocardia with situs inversus will experience the pain of acute appendicitis in the left lower quadrant rather than the right lower quadrant. The diagnostic importance of recognizing this anomaly has obvious surgical implications.

Congenitally Corrected Transposition of the Great Vessels

In uncorrected D-transposition of the great vessels (D-TGV), the aorta arises from the anatomic right ventricle; in corrected L-transposition of the great vessels (L-TGV), the venae cavae drain into the right atrium, which empties into an anatomic left ventricle through a mitral valve. The anatomic left ventricle ejects into the pulmonary artery (PA). In this form of transposition, the atrioarterial connections are concordant, and therefore systemic venous return enters the lung for oxygenation, and pulmonary venous return enters the left atrium and passes into an anatomic right ventricle through a tricuspid valve. Saturated blood then enters the aorta from the anatomic right ventricle. Without another major structural anomaly such as a ventricular septal defect (VSD) with or without pulmonic stenosis, patients with L-TGA may be entirely asymptomatic. There may be people with L-TGA who remain undiagnosed. However, there are a number of known associations with L-TGA, including complete heart block, VSD, pulmonic stenosis, left-sided atrioventricular (AV) valve regurgitation, Ebstein's anomaly of the tricuspid valve, and other complex lesions. Complete heart block may result from the abnormal alignment of the ventricles and interventricular septum. This malalignment of the connection between the bundle of His and the AV node may worsen as the heart grows with a loss of continuity between the two structures and resulting third-degree or complete heart block. Eventually, these patients may

require a permanent pacemaker. With L-TGA, the morphologic right ventricle (systemic ventricle) is at risk of depressed function. There is also a risk of bacterial endocarditis secondary to left AV valve regurgitation. The long-term function of the anatomic right ventricle as the systemic ventricle remains controversial. By 45 years of age, 67% of adults with L-TGA with associated anomalies such as ASD or VSD have developed congestive heart failure (CHF). Even without associated anomalies, approximately 25% of patients with L-TGA will have developed CHF by 45 years of age. To decrease complications from L-TGA, the "double switch" procedure can be performed in which the venous return is transposed using an atrial switch procedure and either the ventricular or arterial connections are transposed via a Rastelli procedure or an arterial switch procedure. In caring for the patient with L-TGA undergoing noncardiac surgery, one must consider the possibilities for disturbances in AV conduction, the ventricular function, and the risk of endocarditis. A preoperative ECG should be obtained, with intraoperative and postoperative ECG monitoring performed. For patients with 2:1 heart block (second-degree block), it may be prudent to place a temporary transvenous or transesophageal pacemaker. If the ventricular function is impaired, arterial line and/or transesophageal echocardiographic monitoring may be warranted.

Congenitally Bicuspid Aortic Valve

A congenitally bicuspid aortic valve may result from abnormal differentiation of the primitive truncal valve, leaving two of the aortic valve cusps fused together, producing a bicuspid instead of tricuspid valve. The bicuspid aortic valve orifice is eccentric and opens in an abnormal fashion. The abnormal orifice produces varying degrees of obstruction, which results in stenosis and increased flow velocity with a systolic ejection murmur. The risk to the patient with a bicuspid aortic valve undergoing noncardiac surgery is determined by the degree of stenosis of the valve and the ventricular function. Bacterial endocarditis is also a risk factor and prophylactic antibiotics should be considered. For patients with severe bicuspid aortic stenosis, balloon valvuloplasty may substantially reduce the gradient across the valve and offer significant symptomatic relief. Balloon valvuloplasty is only an option if the valve is thin and mobile. Adult patients with severe fibrocalcific bicuspid aortic stenosis account for 50% of the surgically significant cases of aortic stenosis. These patients are similar to patients with acquired aortic stenosis with calcific disease of a trileaflet valve and incur similar surgical risks and anesthetic management. Calcific bicuspid aortic stenosis is even less amenable to balloon valvuloplasty than a calcified, stenotic trileaflet valve. However, in the age of transcatheter aortic valve replacement (TAVR), these patients may be candidates for a minimally invasive replacement which leaves them open in the future for a valve in a valve replacement with the deferral of open cardiac surgical intervention. As with all adults with congenital heart disease, it is important to consider the possibility of acquired coronary artery disease (CAD), and it is advisable to screen these patients for CAD. It needs to be determined whether angina is secondary to CAD or solely to the aortic stenosis with the increased oxygen demands of the hypertrophied left ventricle. For patients with bicuspid aortic stenosis, appropriate preoperative evaluation and optimization will help decrease the perioperative risk factors. Intraoperative management should be guided by the patient's functional status and the complexity of the surgical procedure. Conventional monitoring and the use of arterial line, pulmonary artery catheter (PAC), and transesophageal echocardiography may be useful in guiding perioperative therapy. Patients must be monitored for signs of ischemia and ventricular dysfunction. Also, acute decreases in SVR will not be compensated by an increase in stroke volume secondary to the fixed left ventricular outflow tract (LVOT) obstruction.

Volume losses and hypotension must be promptly treated. Volume replacement should be pursued cautiously to avoid pulmonary edema which may result depending on the functional sta-

tus of the left ventricle or systemic ventricle. Pharmacologic support of SVR and ventricular dysfunction may be necessary with inotropes. The requirement of inotropic support is best guided by the previously mentioned monitoring modalities.

Patients with bicuspid aortic stenosis are also at risk for aortic regurgitation secondary to the thickened, calcified leaflets that may become incompetent secondary to their immobile nature. The bicuspid aortic valve may also become incompetent secondary to poststenotic aortic root dilatation. Aortic regurgitation imposes a volume load on the already pressure-overloaded systemic ventricle, which may further impair ventricular function and increase the risk of bacterial endocarditis. In patients with impaired ventricular function, the mode of aortic valve replacement needs to be considered with either surgical replacement or TAVR.

Coarctation of the Aorta

Coarctation of the aorta occurs in 8–10% of all congenital heart defects. It is more common in males than females, with a ratio of 2:1. Patients with Turner's syndrome have a 30% incidence of coarctation. Coarctation is an obstructive lesion that may present early and acutely in the neonatal period as critical coarctation (approximately 9% of coarctation cases) or may be detected later in life as an incidental finding, manifesting as right upper extremity hypertension with diminished lower extremity pulses. The majority of coarctations are located close to the insertion of the ductus arteriosus into the aorta. These juxtaductal coarctations are thought in some way to be produced by contraction of the arterial wall musculature that occurs with constriction of the ductus early in the neonatal period. This may account for the acute presentation of systemic hypoperfusion in affected neonates. Other forms of coarctation are not as easily explained. Coarctation may have only mild gradients at rest, but the gradient will significantly increase with any hyperdynamic state. Unrelieved coarctation leads to upper extremity hypertension, and the consequence of sustained hypertension secondary to coarctation is that the arteries of the head and neck as well as the coronary arteries are exposed to an increased risk of developing atherosclerotic changes. The ventricular myocardium also hypertrophies, increasing the demands on the coronary arteries. The diminished pulsatility of the blood flow distal to the coarctation promotes renal secretion of renin and angiotensin, which may further promote hypertension. The most common sequelae are systolic hypertension, recurrent or residual coarctation, aortic aneurysm, aortic dissection, intracranial aneurysm, and intracranial hemorrhage secondary to intracranial aneurysm formation and sudden death. Due to the significant long-term sequelae and potential disastrous comorbidities, it is of the upmost importance to repair coarctation in a timely fashion. The longer the delay in treatment, the greater the risk of persistent hypertension after the repair. Additionally, the actual life expectancy is significantly reduced, the longer the lesion is left untreated. The overall survival after repair is 91% at 10 years, 84% at 20 years, and 76% at 30 years. For patients who have undergone surgical repair, 30% will have hypertension with a higher incidence than those repaired within the first years of life. If a coarctation is treated within the first few years of life and no significant gradient persists, the patients are expected to be able to lead essentially normal lives.

The surgical approaches to coarctation repair include resection of the stenotic area with direct end-to-end anastomosis, subclavian flap aortoplasty, or aortoplasty with a homograft or synthetic graft material. All of these techniques require the use of aortic cross clamping around the area of coarctation, with the surgical risks of paraplegia or paresis secondary to spinal cord ischemia. Residual obstruction or re-coarctation occurs in 6–33% of all patients. The manner in which residual obstruction or re-coarctation is treated is dictated by the severity and anatomic location of the stenosis. Minimally invasive, catheter-based techniques have become the standard of care and are frequently required more than once in a given patient. Stented graft placement and balloon angioplasty of the aorta are the most common therapy required after the initial surgical repair.

Patients with a history of coarctation both unrepaired and repaired also require the following issues to be considered perioperatively:

- The potential presence and functional status of a concomitant bicuspid aortic valve (as many as 85% of patients with coarctation will have a bicuspid aortic valve)
- The presence of hypertension
- Systemic ventricular function
- The potential for premature or concomitant CAD
- The need for lifelong bacterial endocarditis prophylaxis

In addition to a complete history and physical examination, an ECG, echocardiogram, and ventricular stress test will provide a preoperative assessment of myocardial function, ventricular hypertrophy, and potential for ischemia. The patient with coarctation at the highest risk undergoing a procedure is the older patient with coexisting stenotic or an incompetent bicuspid aortic valve, depressed systemic ventricular function, and acquired CAD. If the patient is to undergo a surgical procedure and it is not urgent, intervention including coarctation repair, aortic valve replacement, coronary artery bypass or angioplasty/stenting, and medical management of the hypertension and depressed ventricular function may be undertaken to decrease the operative risk and provide optimal patient management. In patients with sequelae secondary to coarctation including systemic hypertension and depressed ventricular function, an arterial line and PAC placement are recommended to guide perioperative management. Depending on the degree of ventricular function impairment, intraoperative transesophageal echocardiography (TEE) may be helpful.

Pulmonic Stenosis

Pulmonic stenosis (PS) is an obstructive lesion of the right ventricular outflow tract that produces a pressure overload situation and compensatory changes associated with such lesions. Pulmonic stenosis may be subvalvular, valvular, or supravalvular. PS may also occur near the bifurcation and involve the branch pulmonary arteries. PS may be an isolated lesion or occur as an associated lesion with other complex malformations (tetralogy of Fallot) or as part of a syndrome such as Williams syndrome or Rubella syndrome and others. Mild PS generally causes no major hemodynamic perturbations. However, if the stenosis is severe, right ventricular hypertrophy and dysfunction may ensue. Most importantly for the patient undergoing a procedure are the limitations of compensatory responses of the systemic circulation to critical hemodynamic changes such as hypovolemia. In the case of mild PS, the risk of endocarditis exists with little hemodynamic compromise. However, for patients with severe PS and with impaired right ventricular function, their hemodynamics may be significantly improved with balloon valvuloplasty if the lesion is amenable to intervention. For emergent procedures in patients with severe pulmonic stenosis, perioperative arterial line monitoring and central venous pressure monitoring may be beneficial. Intraoperative transesophageal echocardiography (TEE) should be used for patients with PS and right ventricular or biventricular dysfunction in which loading conditions and ventricular function monitoring are required but in whom a PAC is not an option.

Primary Pulmonary Hypertension and Pulmonary Vascular Disease

Primary pulmonary vascular disease or primary pulmonary hypertension (PPH) is characterized by a decrease in the cross-sectional area of the pulmonary vascular bed caused by pathologic changes in the vascular tissue. PPH is characterized by progressive, irreversible vascular changes similar to those seen in Eisenmenger syndrome but without intracardiac anomalies. PPH is extremely rare in pediatric patients and is primarily a condition of adulthood and is more prevalent in women. It has a poor prognosis and may progress to a cyanotic condition with biventricular heart failure. Pulmonary vascular disease results

from any process that produces prolonged elevation of PA pressure, such as large left-to-right shunts, obstructive airway disease, and chronic lung disease with hypoxia, and causes progressive medial hypertrophy of the pulmonary vasculature with an ultimate decrease in the cross-sectional area. The cause of PPH is not fully understood, but endothelial dysfunction of the pulmonary vascular bed may be an important factor. If severe pulmonary hypertension develops suddenly in the face of an unprepared or non-hypertrophied right ventricle (RV), right-sided heart failure will result. In patients with chronic pulmonary hypertension, gradual hypertrophy and dilatation of the RV develop and the RV pressure may ultimately exceed the systemic pressure.

A decrease in cardiac output may result from at least two mechanisms: (1) A volume and pressure overload of the RV impairs cardiac function, primarily by impaired coronary perfusion of the hypertrophied and dilated RV and decreased left ventricular (LV) function resulting from the dramatic leftward shift of the interventricular septum caused by increasing RV volume. The latter also alters LV structures and decreases LV compliance, resulting in an increase in both LV end-diastolic pressure and left atrial (LA) pressure. (2) The second mechanism may result if a sudden increase in PVR occurs with decreased pulmonary venous return to the LA and hypotension and circulatory shock results as a consequence. Pulmonary edema can occur with or without elevation of the LA pressure. Direct disruption of the walls of the small arterioles proximal to the hypoxic/constricted arterioles may be responsible similar to the mechanism which is proposed for high-altitude pulmonary edema.

Irrelevant of the cause, the clinical manifestations of pulmonary hypertension are similar when significant hypertension exists. The patient's history will often reveal dyspnea, fatigue, and syncope on exertion. A history of CHD or CHF in infancy is present in most cases of Eisenmenger syndrome. Some patients may have a history of angina and headache. Hemoptysis is a late and occasionally fatal manifestation. Cyanosis with or without clubbing may be present. The neck veins may be distended with signs of right-sided heart failure such as hepatomegaly and ankle edema. The ECG will likely show right-axis deviation secondary to RVH, and right atrial enlargement may manifest as arrhythmias occurring in the later stage.

PPH and other types of pulmonary vascular disease are difficult to treat and nearly impossible to reverse unless the etiology is eliminated. Measures to remove or treat the underlying cause include timely surgical correction of the congenital heart defects such as ventricular septal defects (VSDs) or patent ductus arteriosus (PDA) before obstructive anatomic changes occur in the pulmonary vessels. The anesthetic management of pulmonary hypertension is guided by the underlying cause. Strategies for the intraoperative management including cases requiring cardiopulmonary bypass (CPB) and non-bypass cases need individualized assessment. The incidence of symptomatic pulmonary hypertension after repair of an intracardiac lesion does not often justify the placement of pulmonary artery catheters (PACs); however, centers that are familiar with their use have low associated morbidity. The most common strategies to manage pulmonary hypertension include avoiding maneuvers which elicit vasoconstrictive responses, maintaining oxygenation to lower pulmonary vascular resistance (PVR), maintaining alkaline pH, minimizing tidal volumes or using spontaneous modes of ventilation, and the use of pulmonary vasodilators such as nitric oxide, inhaled prostacyclin (PGI_2), and, in the ICU, oral sildenafil. Nitric oxide is a direct pulmonary vasodilator with no significant systemic effect as it is rapidly metabolized by red blood cells. Nitric oxide is administered by inhalation with a special delivery system which can be added to a ventilator or anesthesia machine.

Noncardiac surgery or procedures for patients with PPH, PH, or PVD can be formidable. Fixed or elevated PVR may limit perioperative hemodynamic compensation. The potential for hypotension, RV or biventricular dysfunction, and hemodynamic instability is significant. An abrupt fall in systemic vascular resistance (SVR) may precipitate intense cyanosis. An intraoperative arterial line and PAC monitoring are recom-

mended. In patients in whom placing a PAC is not feasible or in whom the risk of arrhythmia, RA/RV perforation, or PA rupture is believed to be unacceptably high, a TEE may be important in accessing loading conditions, in evaluating biventricular function and the magnitude of right-to-left shunting and air embolism, and in estimating PA pressures from the tricuspid regurgitant jet. TEE must be performed and interpreted by a qualified practitioner in all settings. The perioperative assessment of volume status and necessity for circulatory with inotropes is critically important in the patient with PH. The use of regional anesthesia for patients with pulmonary hypertension is recommended if appropriate for a given procedure as long as the patient does not have associated sedation which incurs significant hypoventilation. In the case of a general anesthetic, appropriate hemodynamic monitoring, airway and ventilatory management along with an appropriate depth of anesthesia will decrease the risk of perioperative instability.

Left-to-Right Shunt Lesions

Patent Ductus Arteriosus

A patent ductus arteriosus (PDA) is a persistent communication between the left PA and the descending aorta, which is approximately 5–10 mm distal to the origin of the left subclavian artery. It is a normal fetal structure and generally undergoes functional closure in the early neonatal period and becomes the ligamentum arteriosum. If the PDA does not close, persistent shunting occurs between the aorta and the PA. A PDA occurs in 5–10% of all congenital heart lesions, excluding premature infants. It is more common in females than males, with a male-to-female ratio of 1:3. A PDA is an extremely common problem among premature infants as a component of persistent fetal circulation and may require interventional catheter-based closure or surgical ligation if it results in respiratory failure or CHF. Patients are generally asymptomatic if the ductus is small. However, a large shunt may predispose patients to lower respiratory tract infections, atelectasis, pulmonary hypertension, bacterial endocarditis, and CHF. Adult patients with PDAs may have developed pulmonary hypertension and pulmonary vascular disease with right-to-left shunting and cyanosis. Paradoxical emboli and stroke are also significant risks for patients with PDA. Therefore, the existence of a PDA is an indication for closure either by transcatheter approach or surgical ligation. The presence of severe pulmonary vascular disease and PH may be a contraindication for closure.

Atrial Septal Defects

Atrial septal defects (ASDs) or ostium secundum ASD occurs as an isolated anomaly in 5–10% of all CHD. It is more common in females than males with a male-to-female ratio of 1:2. Thirty to fifty percent of pediatric patients with CHD have an ASD as an associated defect. Three types of ASDs exist, including secundum, primum, and venosus defects. A patent foramen ovale (PFO) in ordinary circumstances does not cause intracardiac shunting although in certain conditions such as high right-sided heart pressures it may. Ostium secundum defects are the most common type of ASD, accounting for 50–70% of all ASDs. This defect allows for left-to-right shunting of blood from the LA to the RA. Primum defects occur in approximately 30% of all ASDs, including those existing as complete endocardial cushion defects. Isolated primum defects occur in approximately 15% of ASDs. Sinus venosus defects occur in about 10% of all ASDs and are most commonly located at the entry of the superior vena cava (SVC) into the RA. The right pulmonary veins may anomalously drain into the RA and rarely at the entry site of the inferior vena cava (IVC). Spontaneous closure occurs before 18 months of age in more than 80% of patients with defects less than 8 mm. An ASD with a diameter greater than 8 mm rarely closes spontaneously. If a defect is left untreated, CHF and pulmonary hypertension may develop in adults in their 20s and 30s. Patients are at risk for atrial arrhythmias such as atrial fibrillation or flutter, paradoxical emboli and stroke, and rarely bacterial endocarditis.

Device or surgical closure is indicated for patients with left-to-right shunts with a (Q_p/Q_S) of more than 1.5:1. Some physicians consider a smaller shunt to be an indication for intervention because of a risk for paradoxical emboli and stroke. Severe pulmonary vascular disease or high PVR is considered a contraindication for closure. An isolated secundum ASD occurring in an otherwise healthy young adult without pulmonary vascular disease/pulmonary hypertension incurs little additional risk during noncardiac surgery. However, there are two conditions in which difficulties could arise: paradoxical embolization of air or other materials which could stream across the ASD into the system and potentially cerebral circulation. Also, in response to hemorrhage or hypovolemia, there is a compensatory increase in SVR with the decrease in venous return; this situation could worsen a left-to-right shunt.

With time, the large left-to-right shunt decreases pulmonary compliance and increases the work of breathing. The right side of the heart becomes enlarged with both diastolic and systolic dysfunction developing. The LV becomes less distensible and this may worsen the left-to-right shunt. In the fourth decade of life, there is an increase in the incidence in atrial arrhythmias especially atrial fibrillation, atrial flutter, and supraventricular tachycardia. A baseline ECG should be obtained in patients with a history of ASD. The majority of adults older than 35 years of age will frequently be symptomatic from a secundum ASD with at least moderate PH or PVD and RV dysfunction as a result of the chronic left-to-right shunt. For adult patients undergoing cardiac surgery for repair of an ASD, an arterial line, central venous line, and TEE monitoring are recommended. For patients undergoing device closure of their ASD, sedation with intracardiac echo may be recommended or general anesthesia with TEE monitoring may also be undertaken. An arterial line and central line are generally not necessary for device closure. For patients undergoing noncardiac surgery, the monitoring required is generally dictated by the severity of their pulmonary hypertension. For patients with severe PH undergoing a major surgical operation, an arterial line, central venous pressure monitoring, and TEE are recommended. TEE in this situation would be valuable in accessing loading conditions, biventricular function, and the presence and magnitude of shunting. PACs are generally not recommended due to the propensity to cross the atrial septal defect into the left heart. Also, patients with ASDs frequently have valvular regurgitant lesions of the tricuspid, pulmonary, and mitral valve and require bacterial endocarditis prophylaxis.

Ventricular Septal Defects

Ventricular septal defects (VSDs) are the most common form of congenital heart disease and account for 15–20% of congenital heart defects, not including those VSDs which coexist with cyanotic heart lesions. Perimembranous defects are the most common defects accounting for 70% of VSDs. With a small restrictive defects, patients may remain relatively asymptomatic until early adulthood. With moderate to large unrestrictive defects, patients will have delayed growth and development and decreased exercise tolerance, recurrent pulmonary infections, and CHF. Spontaneous closure occurs in 30–40% of patients with membranous VSDs during the first 6 months of life. CHF develops in infants with large unrestrictive VSDs at approximately the first 6–8 weeks of life. Pulmonary vascular occlusive disease may begin to develop as early as 6–12 months of life in patients with unrestrictive defects, but the resulting right-to-left shunt or Eisenmenger syndrome usually does not develop until the teenage years. As mentioned earlier, VSD is the most common form of CHD in childhood. However, certain unrepaired forms of CHD are rarely found in adulthood and VSDs are among them. There are occasional instances when patients with small to moderate-sized, restrictive VSDs present in adulthood.

The repair of VSDs in the adult population may be undertaken in an open surgical fashion or more commonly with a device closure. The degree of pulmonary hypertension or pulmonary vascular occlusive disease will dictate whether the clo-

sure can be performed. For noncardiac surgery the risk is low and related to the magnitude of the left-to-right shunt and to the compensatory response of the LV to the volume overload. Patients with unrestrictive VSDs, who have survived to adulthood, usually do so because an increase in PVR reduces the left-to-right shunt and the volume overload to the LV but achieves a reversed shunt. Very few patients with unrepaired, unrestrictive VSDs survive to adulthood due to the rapid development of PVD, Eisenmenger syndrome, and biventricular failure. Patients with repaired or unrepaired VSDs should be managed and monitored as mentioned previously in the discussion of pulmonary vascular disease. Bacterial endocarditis prophylaxis should be given to both patients with repaired and unrepaired VSDs. Patients with VSDs may have valvular heart disease as a consequence of compensatory intracardiac changes or surgical interventions. Arrhythmias and varying degrees of heart block may be present, including right bundle branch block (RBBB), which occurs in less than 10% of patients and may be a cause of sudden death. Complete heart block occurs in less than 5% of patients. Residual shunts occur in 20% of repaired patients with VSDs and if hemodynamically significant may result in pulmonary hypertension Canneson et. al (2009).

Cyanotic Congenital Heart Disease

Patients with cyanotic CHD are hypoxemic with arterial desaturation which results from shunting of systemic venous blood into the arterial circulation. The severity of hypoxemia and desaturation is determined by the magnitude of the shunting. Most patients with cyanotic CHD do not survive to adulthood without surgical intervention or palliation. In adults with cyanotic CHD, the most common causes are tetralogy of Fallot and Eisenmenger syndrome.

Tetralogy of Fallot

Tetralogy of Fallot (TOF) occurs in 10% of all CHD. It is the most common cyanotic heart defect seen in children after infancy and is the most common form of adult cyanotic CHD. TOF is characterized by a large subarterial VSD, an aorta that overrides the left and right ventricles, right ventricular outflow tract (RVOT) obstruction, and right ventricular hypertrophy (RVH). The RVOT obstruction may be subvalvular, valvular, and supravalvular or in the branch pulmonary arteries. There are also several associated anomalies with TOF, including pulmonary atresia, a right-sided aorta, and ASD, which occurs in 10% of patients and is referred to as pentalogy of Fallot. Coronary anomalies occur in 10% of patients. Patients with TOF are cyanotic secondary to right-to-left shunting. Secondary to the large VSD, the right and left ventricles have equalized pressures. Right-to-left shunting of the venous blood occurs because of increased resistance to pulmonary blood flow secondary to the RVOT obstruction. The severity of the RVOT obstruction determines the magnitude of shunting and therefore cyanosis. The resistance to flow across the RVOT is relatively fixed, and thus changes in SVR affect the magnitude of right-to-left shunting. A decrease in SVR worsens the right-to-left shunt, whereas an increase in SVR decreases the right-to-left shunting. In managing a patient with TOF, it is imperative that the SVR be maintained so the hypoxemia is not worsened.

Patients with TOF generally have cyanosis starting within the first year of life. These children exhibit what is referred to "tet spells" or hypercyanotic spells. These sudden hypoxic episodes are characterized by tachypnea and severe cyanosis with occasional loss of consciousness, seizures, cerebrovascular accidents, and even death. Tet spells do not occur in adolescents or adults. Adults with TOF have dyspnea and very limited exercise tolerance. They also have multisystemic complications of chronic cyanosis, including erythrocytosis, hyperviscosity, renal dysfunction, uric acid metabolism disturbances/gout, hemostatic derangements, cerebral abscesses, strokes, and endocarditis. Most patients with TOF who have not undergone surgical repair or palliation die in childhood. The survival rate is 66% at 1 year of age, 40% at 3 years of age, 11% at 20 years of age, 6% at 30 years of age, and 3% at 40 years of age.

In the past, infants with TOF underwent one of the three palliative procedures to increase pulmonary blood flow with a direct arterial-to-venous shunt (systemic to PA). This serves to increase pulmonary blood flow, decrease cyanosis, and improve exercise tolerance. These shunt procedures included the Waterston procedure (ascending aorta to PA anastomosis), the Potts procedure (descending aorta to left PA anastomosis), and the Blalock–Taussig shunt (subclavian artery to PA anastomosis). These procedures were often associated with long-term consequences such as pulmonary hypertension, PA distortion, and LV volume overload. At present, complete surgical repair with closure of the VSD and relief of the RVOT obstruction is usually performed. Palliative shunting, balloon valvuloplasty, and RVOT stenting are generally only performed on children with unfavorable PA anatomy or those too small or ill to undergo complete repair.

Adult and pediatric patients who have undergone repair of TOF are at risk for other long-term sequelae. Pulmonary regurgitation and/or stenosis may develop as a consequence of surgical repair of the valve or the RVOT with result RVH and RV dysfunction. Repair or replacement of the pulmonary valve may be required either by a surgical approach or more commonly by a transcatheter or hybrid approach. Aneurysm formation at the site of the RVOT repair is not uncommon in repaired TOF patients and has a risk of rupturing. Patients also frequently experience residual or recurrent obstruction of the RVOT and require re-intervention either by surgical or interventional cardiology technique. Ten to twenty percent of patients with repaired TOF have residual VSDs and may be at risk for developing pulmonary hypertension and require repeat surgery. Aortic regurgitation is also a common postrepair finding secondary to the location of the subarterial VSD. Right bundle branch block and other conduction disturbances are common after TOF repair. Complete heart block is a rare complication that requires a permanent pacemaker. All patients with TOF, both repaired and unrepaired, are at risk for endocarditis and should receive SBE prophylaxis before dental or surgical procedures Perloff & Warner (2001).

Ebstein's Anomaly

Ebstein's anomaly of the tricuspid valve occurs in less than 1% of all congenital heart defects. Ebstein's anomaly is a congenital defect of the tricuspid valve in which the septal leaflet and occasionally the posterior leaflet are displaced into the right ventricle and the anterior leaflet is usually redundant, malformed, and abnormally adherent to the right ventricular free wall. As a result, a portion of the right ventricle is "atrialized" in that it is incorporated into the RA and a functional hypoplasia of the RV results. Redundant tricuspid valve tissues can occasionally obstruct the RVOT, and tricuspid regurgitation (TR) or tricuspid stenosis is frequently present. The RA is dilated and hypertrophied and patients are prone to arrhythmias. Eighty percent of patients with Ebstein's anomaly have an ASD or patent foramen ovale (PFO) by which right-to-left shunting may occur.

In the case of Ebstein's anomaly, the severity of the hemodynamic compromise is dependent on the functional status of the tricuspid valve leaflets. Patients with mild apical displacement of the tricuspid leaflets have virtually normal valvular function, whereas those with severe tricuspid leaflet displacement or abnormal anterior leaflet attachment, with valvular dysfunction, have elevated RA pressure and right-to-left interatrial shunting. Likewise, the clinical presentation of Ebstein's anomaly varies from severe cyanosis and heart failure in a fetus or neonate to the absence of symptoms in an adult in whom it is discovered as an incidental finding.

Intrauterine mortality is high for the fetus with Ebstein's anomaly. Neonates with severe disease have cyanosis with heart failure and a murmur noted in the first few days of life. As PVR decreases, there may be a transient improvement, but the condition worsens after the ductus arteriosus closes, thereby decreasing pulmonary blood flow. Older children with Ebstein's anomaly often come to medical attention when a murmur is found on physical exam. Adolescents and adults frequently present with supraventricular tachycardia (SVT) and other arrhythmias. For patients with paroxysmal atrial tachycardia, cya-

nosis, and cardiomegaly, these are the factors which are most closely associated with poor outcome. In patients with Ebstein's anomaly with ASD or PFO, there is a risk of paradoxical embolism, brain abscess, and sudden death. On physical exam patients may have severe cyanosis, hepatomegaly due to passive congestion and elevated RA pressures. Frequently, these patients have large P waves on ECG as well as right bundle branch block (RBBB) and first-degree heart block. Approximately 20% of patients with Ebstein's anomaly have Wolff–Parkinson–White (WPW) syndrome, which is a ventricular preexcitation arrhythmia through an accessory pathway between the atrium and the ventricle. A delta wave may be present on ECG.

For adult patients with Ebstein's anomaly who are symptomatic despite medical management, it is recommended to undergo repair or replacement of the tricuspid valve and closure of the ASD. Surgery may also be recommended for patients with less severe symptoms but whom also have cardiomegaly. For patients undergoing both cardiac surgical intervention and noncardiac surgery, it is recommended that all patients have complete perioperative evaluation and optimization including appropriate imaging such as echocardiogram and/or MRI as well as ECG. Perioperative arterial line and central venous pressure monitoring are recommended as well as intraoperative TEE. TEE monitoring is recommended to evaluate anatomy, shunting, loading conditions, biventricular function, the presence of RVOT obstruction, the presence of associated anomalies, loading conditions, and the integrity of the repair in the case of cardiac surgery. PAC monitoring is not recommended as it is likely to cross the ASD into the left heart.

Transposition of the Great Arteries

D-Transposition of the great arteries (D-TGA) occurs in about 5% of all CHD with a male predominance of three males to one female. D-TGA exists when there is an anatomic discordance between the ventricles and the great arteries, in that the morphologic RV gives rise to the aorta and the morphologic LV gives rise to the PA. The physiologic consequence, surgical plan, and long-term sequelae are contingent on the age at presentation and the associated anomalies. If the systemic and pulmonary venous returns are normal, the alternatives for surgical correction have traditionally been "switching" the circulation at the great arterial level (arterial switch or Jatene procedure) or at the atrial level (Senning or Mustard procedure). For patients with D-TGA, VSD, and subpulmonic stenosis, the Rastelli procedure realigns the ventricular septum so that the appropriate venous return is associated with the correct great vessel and the subpulmonic stenosis is resected. Patients with associated defects such as aberrant venous return and RVOT or LVOT obstruction (occurs in 30% of patients) require a customized plan for correction or palliation. Additionally, 30% of patients with D-TGA have coronary anomalies including the origins of the coronary arteries and the sinuses of Valsalva, which are displaced to the posterior portion of the transposed aorta. This represents a risk for coronary compromise and ischemia as a short- and long-term consequence of arterial switch procedures. VSDs of hemodynamic significance are also associated with 25% of D-TGA patients Hucin et al. (2000).

Prior to the introduction of the atrial baffle procedures (Senning and Mustard operations), the 1-year mortality for patients with D-TGA was approximately 90%. The Senning and Mustard interatrial baffle procedures were developed in the late 1950s and early 1960s and significantly improved survival for patients with D-TGA. Many of these patients now comprise a significant portion of the adult congenital population. The procedures attempt to correct the circulation which runs parallel by redirecting venous return at the atrial level. Systemic venous blood enters the RA and is directed across the atrial septum through the baffle and across the mitral valve to the LV and into the PA. Similarly, pulmonary venous return is directed across the atrial septum through the tricuspid valve and into the RV and ejected into the aorta. The difference between the two procedures involves aspects related to the atrial septum construction and placement of the suture lines, which have had long-term sequelae.

Atrial switch procedures have a number of long-term consequences including arrhythmias, sudden death, RV (systemic ventricle) dysfunction, baffle leaks, and obstruction which impairs venous return from the respective circulation. SVT, atrial fibrillation, atrial flutter, and sinus node dysfunction are the most common arrhythmias. Pulmonary hypertension, ventricular dysfunction, and junctional rhythm are risk factors for SVT. Approximately, one third of patients with atrial switch procedures will ultimately require a permanent pacemaker secondary to sinus node dysfunction. Ten percent of patients will experience baffle obstruction of either the systemic or pulmonary venous return. The function of the RV as the systemic ventricle deteriorates with time, and sudden death is experienced in 5% of patients and is attributable to persistent heart failure. Other causes of sudden death in these patients are attributable to arrhythmias and pulmonary hypertension.

For patients with D-TGA, VSD, and subpulmonic stenosis, the Rastelli procedure is frequently performed. In this procedure, the VSD is closed in a manner that redirects venous return to the appropriate great vessel, and an RV to PA conduit is placed to relieve the subpulmonic stenosis. Long-term follow-up in these patients reveals 74% survival for patients operated on in the 1980s. The majority of patients require further intervention both surgical and catheter based. There is also a 5% risk for sudden death in these patients due to ventricular dysfunction and arrhythmias.

The arterial switch operation or Jatene procedure involves transplanting the coronary arteries to the PA and connecting the proximal great vessels to the distal ends of the other vessel in an attempt to restore anatomically correct circulation. This procedure is considered superior to the atrial switch procedures in that it is physiologically correct and results in fewer long-term complications such as arrhythmias, RV failure, baffle obstruction, and TR. For patients with uncomplicated D-TGA, normal sinus rhythm is usually present, and providing good coronary blood flow, LV function is preserved. However, PA stenosis at the site of reconstruction occurs in 5–10% of cases. Complete heart block is a risk in 5–10% of patients, and aortic regurgitation (AR) is a late complication and occurs in 20% of patients especially in patients who underwent PA banding in the neonatal period. An important cause of AR may be unequal size of the pulmonary valve cusps that leads to eccentric valvular coaptation. The most important life-threatening complication associated with arterial switch is the possibility of coronary obstruction which leads to myocardial ischemia, infarction, and death. Long-term outcomes continue to be accessed with many patients who have previously undergone the arterial switch procedure entering their third decade of life. The overall conclusion is that the arterial switch is the procedure of choice with preservation of physiologic circulation but that coronary obstruction, pulmonary stenosis, and aortic insufficiency remain significant problems.

Eisenmenger Syndrome

Eisenmenger syndrome develops over time as a consequence of significant, uncorrected left-to-right shunting in association with a VSD, ASD, or PDA. As discussed previously in this chapter, morphologic transformations occur in the small PAs and arterioles, leading to pulmonary hypertension and the resultant reversal of the intracardiac shunt creating cyanosis. In the small PAs and arterioles, medial hypertrophy, intimal cellular proliferation, and fibrosis lead to narrowing or closure of the vessel lumen. With sustained pulmonary hypertension, insidious atherosclerosis and calcification often develop in large PAs. The initial morphologic alterations, medial hypertrophy of the pulmonary arterioles, intimal proliferation and fibrosis, and occlusion of capillaries are potentially reversible. However, as the disease progresses, the morphologic changes including plexiform lesions and necrotizing arteritis are irreversible and result in obliteration of the pulmonary vascular bed, which leads to increased PVR. As the PVR approaches or exceeds systemic resistance, the shunt is reversed. The morphologic changes in the pulmonary vasculature that occur with Eisenmenger syndrome usually

begin in childhood, but symptoms don't usually start to appear until adolescences or early adulthood when the right-to-left shunt is sustained and cyanosis appears.

Most patients have decreased exercise tolerance and dyspnea and these symptoms may be compensated for a time period. Atrial arrhythmias frequently develop such as atrial fibrillation and atrial flutter. Erythrocytosis develops due to arterial desaturation, and symptoms of hyperviscosity such as visual disturbances, fatigue, headache, dizziness, and paresthesias frequently develop. Hemoptysis secondary to rupture or infarction of dilated PAs can occur and be life-threatening. Patients who have developed cyanosis also have abnormal hemostasis and are at risk for cerebrovascular accidents which can occur due to paradoxical emboli, venous thrombosis, or intracranial hemorrhage. Patients with Eisenmenger are also at risk for brain abscess and syncope. Syncope may occur secondary to inadequate cardiac output or arrhythmias. Symptoms of heart failure are not common until the disease is in advanced stages and implies a very poor prognosis. Patients with Eisenmenger are at risk for sudden death.

Medical management of Eisenmenger syndrome is similar to that of pulmonary hypertension and includes inhaled oxygen, nitric oxide, treprostinil, and IV vasodilators such as epoprostenol. Other dilators such as sildenafil may be taken orally and used in conjunction with calcium channel blockers, endothelin receptor antagonists, anticoagulants, diuretics, and antiarrhythmics. For some patients, the ultimate therapy may be heart–lung transplantation providing other organ systems have preserved function. The effectiveness of these therapies is limited by the severity of the disease. Patients with Eisenmenger syndrome should avoid high-altitude and excessive exertion, dehydration, and the use of systemic vasodilators.

Pregnancy is associated with high maternal and fetal morbidity and mortality. The fixed PVR precludes any compensation for acute fluctuations in SVR, cardiac output, and blood volume during labor, delivery, and the peripartum period. Any acute decrease in SVR precipitates increased right-to-left shunting and results in severe cyanosis. Valsalva maneuvers during labor may acutely increase SVR, depress systemic and cerebral perfusion, and trigger fatal syncope.

Patients undergoing both cardiac and noncardiac surgery should be cared for in centers experienced in the management of such patients and require a multidisciplinary approach. The anesthesia care required is meticulous management of fluid status and both systemic and pulmonary vascular resistance. Maintenance of SVR and contractility, minimizing blood loss and intravascular volume depletion, as well as preventing paradoxical embolization are imperative. Most patients are admitted for overnight IV placement and mild hydration. Prophylactic phlebotomy is generally not done in most centers as the volume shifts may be poorly tolerated. The intraoperative management is frequently dictated by the nature of the procedure; however, most general anesthetic including cardiac procedures will necessitate arterial line and central venous pressure monitoring and TEE monitoring. PACs are not indicated due to the likelihood of crossing the shunt lesion such as an ASD or the potential for PA rupture.

Single-Ventricle Physiology and Complex Cyanotic Congenital Heart Disease

Advances in palliative and corrective heart surgery, catheter-based interventions, anesthesia, and imaging have significantly increased the number of patients with complex, cyanotic heart disease who have reach adulthood. Patients who have undergone single-ventricle palliation with a Fontan procedure illustrate the cumulative risks of dysrhythmias, decreased ventricular function, and chronic hypoxemia as well as other multiorgan system sequelae.

Many complex congenital heart lesions result in anatomic malformations that are not amenable to surgical intervention and result in a functioning biventricular circulation. These lesions include severe Ebstein's anomaly, tricuspid atresia, hypoplastic left heart syndrome (HLHS), unbalanced atrioventricular canal (AV canal), and various

defects associated with heterotaxy syndrome. These forms of CHD require staged procedures that attempt to use an existing ventricle as the systemic ventricle and create a mechanism for pulmonary blood flow that may not necessarily require a pumping chamber and will likely be passive flow. The surgical plan for these patients is somewhat individualized and dependent on the native anatomy with the ultimate conformation relatively similar among patients with single-ventricle physiology. The Fontan circuit functions to direct systemic venous return via a conduit into the PA system. The circuit does not require a right-sided heart chamber, and pulmonary venous blood returns into a common atrium and flows into the systemic ventricle Hosking & Beynen (1992).

The first palliative operation for patients with single-ventricle physiology usually requires a shunt from an arterial source that provides pulmonary blood flow or a ductal stent to maintain an open PDA as the source for pulmonary blood flow in the first-stage hybrid palliation procedure. Adequate mixing at the atrial level is required with an unrestrictive ASD along with unobstructed systemic ventricular outflow. In the past, the Blalock–Taussig (BT) shunt (right subclavian to PA anastomosis) or a central shunt (aorta to PA shunt) was performed. Presently, the modified BT shunt is frequently used with a Gore-Tex conduit from the right subclavian artery to the PA to provide pulmonary blood flow. Historically, the classic BT shunt permanently compromised arterial blood flow to the right arm. The modified BT shunt is generally ligated at the time of the subsequent procedure and does not permanently compromise flow. This is relevant in that patients who have undergone a classic BT shunt will not have an accurate blood pressure measured in the right upper extremity. The BT shunt in the case of HLHS provides the pulmonary blood flow while the creation of a neoaorta (Norwood procedure) from the proximal PA creates the manner in which systemic blood flow leaves the heart. The subsequent procedures in the palliative process attempt to route systemic blood flow to the PA vascular bed. The second-stage procedure (bidirectional Glenn shunt) involves creating a superior vena cava to PA anastomosis. The final stage, or Fontan procedure, results in the creation of an inferior vena cava to PA connection and may be undertaken in a number of ways. Fenestration of the Fontan conduit creates a functional ASD that serves as a pressure outlet in the setting of pulmonary hypertension and maintains LA filling and systemic perfusion Khairy et al. (2007).

Modifications and revisions of the single-ventricle palliative path have been made since their initial performance in the 1970s and decreased the incidence of adverse sequelae such as arrhythmias, pulmonary hypertension, ventricular dysfunction, and heart failure. For patients who underwent the Fontan procedure in the 1970s, the 15-year survival rate was 50–80%. The majority of Fontan patients have NYHA class I or II symptoms and exhibit decreased exercise tolerance. Approximately 40% of these patients require reoperation for conduit obstruction, permanent pacemaker, or AV valve repair for valvular regurgitation. Atrial arrhythmias are very common among Fontan patients, and loss of the atrial contribution to cardiac output can result in significant impairment, and patients will frequently require permanent pacing.

Another significant adverse sequela of Fontan physiology is protein-losing enteropathy (PLE). PLE develops in 5–10% of patients and is manifested by gastrointestinal protein malabsorption, ascites, peripheral edema, pleural effusions, and low serum protein levels. Elevated systemic venous pressure, abnormal mucosal blood flow patterns, and glycosylation of enteric proteins have been implicated as the cause of this condition. Patients with fenestrated versus non-fenestrated Fontan conduits have a decreased incidence of protein-losing enteropathy. The therapies include fenestration of the Fontan conduit, anticoagulation, dietary modifications, corticosteroids, and ultimately heart transplantation.

Following Fontan procedures, the formation of arteriovenous malformations (AVMs) has been observed, especially pulmonary AVMs in the lungs. Pulmonary AVMs produce a significant volume load on the ventricle and impair function. Shunting may also occur through the AVMs and induce parenchymal changes, hypoxia, and poor lung compliance.

The perioperative management of these patients requires attention to maintaining SVR, not increasing PVR and attention to loading conditions and fluid status. High positive pressures with ventilation or other maneuvers which decrease venous return are not recommended. The type of invasive monitoring is dictated by the procedure. For patients undergoing cardiac surgery or procedures, arterial line and central pressure monitoring is recommended. TEE is required to access ventricular function, AV valve regurgitation, potential paradoxical emboli, loading conditions, and the integrity of the repair. For patients undergoing noncardiac surgery, similar monitoring may be advised depending on the procedure. Attention needs to be paid to bleeding or other volume losses with appropriate fluid management or blood replacement. Patients are at high risk for antibodies and type-specific blood may take extra time to prepare.

Perioperative Concerns and Anesthetic Management

The perioperative strategy and management require a complete assessment and consider factors relevant to both the patient's underlying physiology as well as factors related to the proposed procedure. The patient's baseline cardiovascular reserve and underlying multi-organ system impairment must be evaluated in conjunction with the concerns specific to the CHD and potential acquired comorbidities related to aging. The techniques required for the procedure need to be considered and balanced in light of what the patient's cardiovascular reserve will tolerate. For example, a patient with a failing Fontan physiology is unlikely to tolerate high-pressure abdominal insufflation associated with numerous laparoscopic procedures currently being performed. It is recommended that adult patients with CHD be cared for in a center with a dedicated team familiar with their unique physiology and that a multidisciplinary approach be used when faced with complicated medical decisions regarding these patients Landzberg et al. (2001).

Syndromes and Associated Anomalies

Many forms of CHD occur in association with other congenital syndromes and congenital anomalies which are noncardiac. Endocardial cushion defects such as AV canal, ASDs, and VSDs are common among patients with Down's syndrome. These patients have characteristic anomalies which impact management such as developmental delay, hypotonia, large tongue, short necks, potential for atlanto-occipital dislocation, and other features related to the syndrome. DiGeorge syndrome is another association in which conotruncal anomalies occur with abnormal calcium homeostasis, immunodeficiency, and multiple midline craniofacial anomalies. VACTERL association includes vertebral defects, anal atresia, cardiac defects, tracheoesophageal fistula, renal anomalies, and limb abnormalities. Patients with VACTERL association typically have at least three of these defects and require attention to potential other systemic involvement. However, in the adult congenital population, it is likely that other noncardiac defects would have been previously diagnosed Perloff & Child (2008).

Perioperative Monitoring

Perioperative monitoring must be carefully considered and appropriate for the level of baseline impairment and anticipated demands of the procedure. Arterial line, central venous pressure monitoring, and TEE monitoring may be required to ensure the most accurate assessment of loading conditions, biventricular function, direction and magnitude of shunting, and potential for paradoxical embolism. The standard monitoring equipment such as ECG, pulse oximetry, and temperature and noninvasive blood pressure monitors may also require a little extra consideration. For example, the question may arise as to where to place the ECG pads for a patient with dextrocardia or heterotaxy syndrome. The answer is that a 5-lead and 3-lead ECG placement is done in the standard fashion

for all patients (baseline ECGs are also performed in the standard position). For patients who have undergone a coarctation repair incorporating the left subclavian artery, the right upper extremity will most accurately reflect the systemic blood pressure. There may also be a residual gradient between the upper and lower extremity blood pressures in these patients. For patients who have previously undergone a classic BT shunt, the ipsilateral extremity may not accurately reflect the systemic blood pressure as well as oxygen saturation, and an alternative site should be selected. For patients undergoing cardiac surgery, cerebral oximetry is also recommended and considered standard of care.

Airway and Ventilatory Management

Patients with CHD may have associated anomalies including those involving the airway. In the adult population, these anomalies may already be well documented and/or known to the patient or their families. In addition, patients who have undergone previous surgery may have experienced prolonged periods of intubation and mechanical ventilatory support, and the potential for subglottic stenosis and a history of tracheostomy are possibilities. The transition from spontaneous ventilation to positive pressure ventilation can significantly impair preload, secondary to decrease systemic venous return. This is especially important in the scenario of hypovolemia.

Patients with single-ventricle physiology are extremely sensitive to positive pressure ventilation because their pulmonary blood flow is preload dependent. Episodes of desaturation may be an indication that pulmonary blood flow is being compromised. If standard interventions are attempted such as increasing tidal volume or adding positive end-expiratory pressure (PEEP), the result may further decrease in the saturation, secondary to further decrease in pulmonary blood flow. In the case of single-ventricle physiology, maintaining adequate intravascular volume status, limiting the peak inspiratory pressure, and avoidance of PEEP will facilitate pulmonary blood flow and preserve oxygenation.

Intravenous Access Considerations

Intravenous access can often present a significant problem in patients with CHD, especially those who have undergone multiple procedures or who have significant peripheral collateralization secondary to cyanotic heart disease or venous obstruction. A careful examination of the patient may reveal previously cannulated or cut-down sites as well as a review of previous operative reports and cath reports. Ultrasound of the potential sites as well as angiography in the cath lab will help in identifying sites available for vascular cannulation. Patients with right-to-left shunts are at risk for paradoxical embolization of air or particles, even when infused into peripheral lines and vigilance and the use of infusion filters is recommended to decrease the possibility of emboli.

Perioperative Fluid Management and NPO Intervals

Standard NPO intervals in healthy adult patients with normal cardiovascular reserve generally have little impact. However, for patients with cardiac anatomy dependent on adequate filling pressures, even minor decreases in preload can have adverse effects. Patients with single-ventricle physiology, cyanotic patients with erythrocytosis, patients with Eisenmenger physiology, and patients with volume-dependent obstructive lesions are extremely sensitive to acute decreases in preload. Decreased preload and the vasodilating effects of anesthetic agents can lead to acute circulatory collapse even in patients who seem well compensated prior to induction. Ensuring adequate preload prior to induction and judicious titration of anesthetic agents can facilitate preservation of cardiac output in the previously described patients. Management of perioperative volume losses should be guided by the monitoring of vital signs, arterial line pressure, central

venous pressure, hematocrit, urine output, acid–base status, and electrolytes.

Third-space losses, especially in the case of patients with protein-losing enteropathy, must be considered. PLE results in hypoalbuminemia, ascites, and pericardial and pleural effusion and is associated with high systemic venous pressures and ventricular dysfunction of the single ventricle. These patients are frequently total volume fluid overloaded with third-space sequestered volume and intravascular space depleted with poor cardiovascular reserve. This clinical situation implies extremely poor cardiac reserve, and the ability to tolerate or compensate for intravascular depletion, vasodilating anesthetics, and positive pressure ventilation is exceptionally limited. Medication doses should be reduced to account for the effect of hypoalbuminemia, and all medications should be titrated to effect with hemodynamic monitoring. Appropriate first-case scheduling, minimizing NPO intervals, or preoperative hospital admission with IV hydration should be considered in this group of patients, to avoid the risks of intravascular volume depletion.

Hematocrit and Perioperative Transfusion Management

Patients with chronic cyanosis will compensate for their hypoxemia with a baseline erythrocytosis in an attempt to increase oxygen delivery. If a chronically cyanotic patient is found to have a normal range hematocrit, a coexisting anemia, usually iron deficiency, should be considered. Erythrocytosis predisposes patients to complications of hyperviscosity. A hematocrit of greater than 40% is generally considered to provide an adequate red cell mass for oxygen delivery. However, the patient's own baseline hematocrit will frequently serve as a guide, providing they are not anemic.

Extra consideration must be given to the situation in which a transfusion is required in that many patients with CHD require special preparation of blood products. Patients with DiGeorge syndrome or who are immunosuppressed require cytomegalovirus (CMV)-negative blood that has been irradiated and leukocyte filtered. This is done to decrease the potential transmission of CMV and prevent graft-versus-host disease, along with other leukocyte-mediated transfusion reactions. If a question arises regarding the type of blood products required for a specific condition, a hematologist or blood bank pathologist should be consulted. Additionally, the majority of adult congenital heart patients have undergone previous heart surgery with the concomitant exposure to blood products and previous transfusion. It is extremely common for these patients to have developed antibodies that may complicate the cross-match process, and extra time must be allowed in order to prepare type-specific blood products. Attention must also be paid to patients that may in the future require heart transplantation. Limiting transfusions and therefore antibody formation is vital for these patients. Adult congenital heart patients should also receive leukocyte-depleted blood to also help decrease antibody formation.

Antibiotic Prophylaxis

The requirement for SBE prophylaxis is dictated by the underlying cardiac disease and anatomy as well as the type of procedure being performed. The American Heart Association offers a comprehensive list with specific recommendations for patients with CHD on their website www.americanheart.org. Most patients with CHD have significant graft material and prosthetic valves as well as intracardiac shunts and regurgitant or stenotic valves. They are at high risk for endocarditis and it is a frequent complication for many patients with CHD.

Pacemakers and Arrhythmias

Arrhythmias are among the most prevalent and complex sequelae for patients with adult CHD. The arrhythmias and common rhythm disturbances associated with each defect have been previously discussed and can be found with

the respective lesion discussion. Many patients with adult CHD require antiarrhythmic therapy that should be reviewed before surgery. The side effects and interactions of these medications should be known. A baseline ECG is recommended before all procedures, and if arrhythmias do arise in the perioperative period, a rapid diagnosis should be made and therapy should be instituted. The underlying etiology should be considered in each case with respect to the circumstances and underlying anatomy and physiology. For example, D-TGA with atrial switch anatomy is known to be associated with atrial arrhythmias. Electrolyte disturbances especially secondary to diuretic therapy, hypercarbia, acidosis, severe hypoxia, and antiarrhythmic agents can also produce arrhythmias. Medications that blunt vagal tone should be used with extreme caution.

Many patients with adult CHD have permanent pacemakers and implantable cardiac defibrillators (ICD). The settings and the underlying rhythm should be known. A magnet for conversion to the asynchronous mode should be available, and the therapy mode of the ICD may need to be deactivated to avoid triggering inappropriately in the operative setting.

Postoperative Considerations

In the immediate postoperative period, extreme vigilance and similar levels of monitoring which were employed during the operative period should be continued. The level of postoperative monitoring should be appropriate for the patient's baseline physiology and the nature of the surgical procedure and its anticipated postoperative sequelae. Many patients with adult CHD will continue to need arterial line and CVP monitoring in the postoperative period and may require management in the intensive care unit that an otherwise normal cardiovascular status patient undergoing the same procedure would not require.

Pain management and postoperative nausea and vomiting are important considerations. Appropriate analgesia including narcotic medications, regional anesthesia which does not impair SVR, acetaminophen derivatives, and nonsteroidal anti-inflammatory medications are all used with success in patients with CHD. Analgesia facilitates improved respiratory mechanics and decreases oxygen consumption. However, respiratory depression, hypercarbia, and airway obstruction must be avoided secondary to their significant effects on increasing PVR. The management of postoperative nausea and vomiting is crucial for oral hydration and the ability to resume medication regimens especially antiarrhythmic and anticoagulation medications.

Conclusion

Adult patients with CHD represent an ever-increasing group of patients with complex cardiac anatomy and physiology as well as acquired comorbidities. These patients represent a challenge to the medical community and require a multidisciplinary team approach with comprehensive perioperative planning. At this time, there are no evidence-based guidelines for the perioperative management of adult patients with CHD. Large-scale clinical trials are required to demonstrate the optimal management strategies, and it is recommended that these patients be cared for in cardiac centers with congenital heart specialists who are familiar with their physiology. An appreciation of the previously discussed principles will assist the provider in evaluating a multitude of structural lesions based on their underlying physiologic effects. Ultimately, an understanding of the patient's unique physiology and multi-organ system sequelae will enhance the likelihood of perioperative cardiovascular stability.

Case Study: Anesthetic Management of a Hybrid Approach to Transcatheter Pulmonary Valve Replacement in a Previously Repaired Patient with Tetralogy of Fallot

A 15-year-old male with a history of TOF s/p transannular patch repair as an infant presents with severe pulmonary valve regurgitation (PR)

and right heart dilatation. Although asymptomatic from a cardiac standpoint, he did have severe right ventricular dilation on MRI (RVEDV = 180 mL/m ^{2}). After careful discussion about treatment options, the patient decided on a transcatheter Melody valve. A diagnostic angiogram showed an extremely enlarged and tortuous pulmonary artery not amenable to a Melody valve. 3D reconstruction of the patient's PA was used to further evaluate the anatomy for other possible interventions. After careful planning and several virtual implants, a hybrid procedure was decided upon in which a Melody valve could be placed within a pulmonary artery stent. In preparation for the hybrid procedure, the patient was premedicated with midazolam and induced with etomidate and cisatracurium for general endotracheal anesthesia. A radial arterial line and right internal jugular central line were placed. Both OR staffing and a perfusionist were on standby to go on cardiopulmonary bypass and convert to an open procedure if necessary. Access for stent delivery was achieved through a subxiphoid incision by a cardiothoracic surgeon. Under fluoroscopy and transesophageal echocardiogram (TEE), a covered stent and landing stent were placed with vascular plugs along the tortuous pulmonary artery taking care not to compromise the branch pulmonary arteries and ensuring good flow through the RVOT. After confirmation of proper seating of the stents, the Melody valve was delivered through the subxiphoid incision and deployed within the landing zone stent in the pulmonary artery. Postdeployment intracardiac echo (ICE), TEE, and angiogram showed no PR and no compromise to the branch pulmonary arteries. The patient was transferred to the PICU where he was extubated after several hours and discharged home the next day (Figs. 1, 2, 3, and 4).

Case Discussion

Surgical repair of TOF has been occurring for about 50 years with excellent outcomes. However, with longer survival, we are seeing more long-term complications of these repairs, specifically pulmonary valve regurgitation. Untreated PR in these patients can result in right-sided remodeling, which if left untreated can lead to right heart failure. Previously, that intervention was not recommended until the patient became symptomatic from the pulmonary regurgitation. However, several studies have shown that early repair of pulmonary valve regurgitation can prevent long-term right heart remodeling.

Fig. 1 3D reconstruction of pulmonary artery

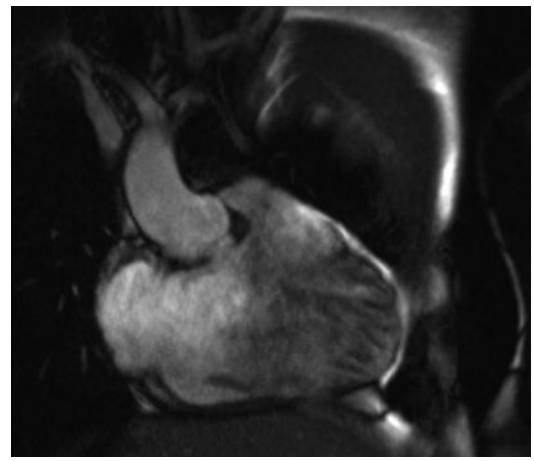


Fig. 2 Cardiac MRI showing dilated right ventricle

Currently, cardiac MRI is the gold standard for measuring right ventricular volume and pulmo-

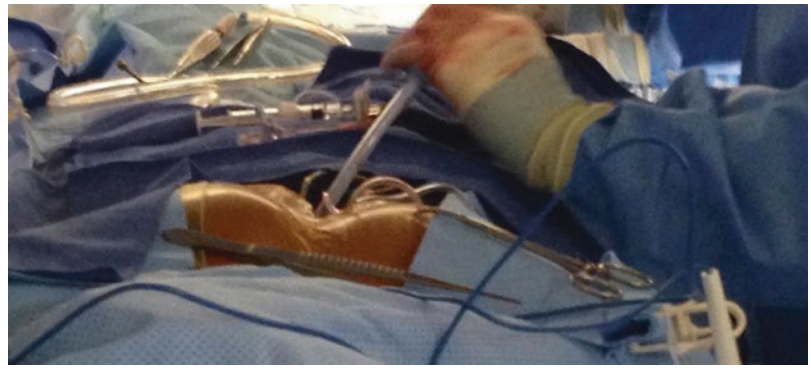


Fig. 3 Subxiphoid access for stent delivery

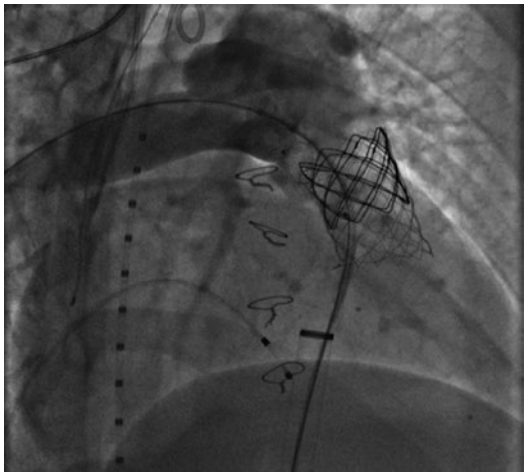


Fig. 4 Angiogram showing post-Melody valve deployment with no pulmonary regurgitation

nary regurgitation. The precise timing of when to intervene is unclear, but studies seem to show remolding of the RV when RVEDV >150 mL/m^2. Despite the overall good outcomes with surgical repair for these patients with pulmonary regurgitation, it is not without its risk factors. Most patients will have significant scar tissue formation with adherent right ventricle to the chest wall, making entering the chest extremely high risk. There are some limitations secondary to unfavorable PA anatomy which may require a hybrid approach with access through a subxiphoid incision to allow for multiple large stent placement and/or better trajectory of valve deployment. General anesthesia and arterial line are mandatory, while central access should be considered depending on the patient's venous access and baseline cardiac function. TEE is used to monitor function, access the pre- and postimplant anatomy, access loading conditions, guide the procedure, and monitor for pericardial effusion. The usual goals for PR physiology should be applied for these cases. Perfusionists and surgical staff should be readily available to go on bypass and convert to an open procedure should complications arise. Complications include bleeding, pulmonary artery rupture, cracked stents, compression of coronary vessels, arrhythmias, pulmonary regurgitation, and stent migration and embolism. Early extubation in the cath lab has been described; however, it may be prudent to leave the patient intubated if there are concerns for bleeding or if there are large fluid shifts related to volume resuscitation. The Melody valve and other transcatheter valves have made repair of pulmonary regurgitation in previously repaired TOF patients much less invasive and ultimately safer. It is important to be aware of the complications that can occur with the hybrid procedure.

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Medical Facility Infrastructure Considerations

Antonio Hernandez Conte

Abstract

The process for identifying pediatric patients, evaluating their health status, and ultimately treating their conditions has grown into an ever increasingly complex endeavor and requires a vast array of infrastructural considerations. In the United States, more than one-third of all patients are referred to a specialist each year. Despite the frequency of referrals and the importance of the specialty referral process, the process itself has been a long-standing source of frustration among both primary care physicians (PCPs) and specialists. Academic medical centers, traditionally tertiary and quaternary care centers housed within a centralized medical facility and associated with a medical school, have been viewed as slightly more integrated models of care. However, many of these centers receive transfers and referrals from outside community hospitals. Linking pediatric patients to specific care has been a major area of focus for the last two decades. Coordination would maximize utilization of co-location, co-management, and networking/information sharing—these would help use existing resources more effectively and improve the quality of care by reducing barriers to care; promoting early referral, linkage, and follow-up; promoting cross-discipline problem-solving and family-centered care; and reducing duplication and fragmentation of services. Centers providing evaluation and treatment of pediatric cardiac and congenital issues must at a minimum possess a wide array of resources involving technological investments and a broad group of highly specialized personnel. Optimal and highly organized care would allow initial evaluation with multiple specialists all in one centralized setting.

Keywords

Pediatric referral networks · Congenital heart evaluation · Quaternary pediatric care Congenital care platform · Hybrid operating rooms · Congenital adult surgeons · Pediatric heart surgeons

During the mid-1800s in the United States, it was recognized that medical and surgical care for the pediatric patient required facilities that were altogether different than those utilized to care for the adult patient. The forward-thinking pediatricians, surgeons, and anesthesiologists of the 1800s would be satisfied to know that their vision of a medical facility dedicated to pediatric

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is just as applicable in the twenty-first century as it was in the 1800s. The process for identifying pediatric patients and patients with congenital disease, evaluating their health status, and ultimately treating their conditions has grown into an ever increasingly complex endeavor and requires a vast array of infrastructural considerations. This chapter will outline the various processes, guidelines, and facility infrastructure requirements that are necessary to optimally care for the pediatric and adult patient with congenital heart disease.

Identification of Pediatric and Adults Patients and Referral Management for Congenital Disease

In the United States, more than one-third of patients are referred to a specialist each year, and specialist visits constitute more than one-half of outpatient visits. Despite the frequency of referrals and the importance of the specialty referral process, the process itself has been a long-standing source of frustration among both primary care physicians (PCPs) and specialists. These statistics hold true for both the adult and pediatric populations. The American College of Cardiology 2008 guidelines for the management of adults with congenital heart disease recommend that care of adults with moderate and complex congenital heart disease (CHD) be guided in collaboration with clinicians trained in adults with congenital heart disease (ACHD) (Warnes et al. 2008). Numerous strategies have been developed and tested in an effort to improve the specialty referral process; these may include the utilization of "gatekeepers of care" or specialty referral guidelines (Mehrotra et al. 2011).

PCPs vary in their threshold for referring a patient, which results in both the underuse and the overuse of specialists. Many referrals do not include a transfer of information, either to or from the specialist, and when they do, the transfer materials often contain insufficient data for medical decision-making. Making matters more complicated, care across the primary care-specialty interface is poorly integrated. Additionally, PCPs often do not know whether a patient actually went to the specialist or what the specialist recommended. PCPs and specialists also frequently disagree on the specialist's role during the referral episode (e.g., single consultation or continuing co-management). Therefore, typically a referral for specialty assessment may lead to a dilemma for parents or caregivers of the pediatric patient. To further complicate the scenario, a significant portion of healthcare delivery systems in the United States are not horizontally or vertically integrated. Therefore, referral processes are even more complex, and information transfer is poor in these instances which can lead to delays in assessment and ultimately life-changing care. For example, A review of data from approximately 90 self-described adult congenital heart disease (CHD) programs in the United States indicates that the number of ACHD patients seen in these specialized clinics is far below targeted estimates; it is likely that a substantial number of adult CHD patients continue to be cared for by pediatric cardiologists (Fernandes et al. 2012).

Barriers to Care

Academic medical centers, traditionally tertiary and quaternary care centers housed within a centralized medical facility and associated with a medical school, have been viewed as slightly more integrated models of care. However, many of these centers receive transfers and referrals from outside community hospitals so many of the same problems exist within quarternary systems. One particular academic institution developed and implemented a networking strategy specifically for pediatric surgery (Coran et al. 1999). The major changes were the addition of a satellite facility, as well as the incorporation of four

additional external practices to the existing university practice. To assess the impact on financial status of the new networking paradigm upon clinical activity, education, and academic productivity, the following parameters were analyzed: gross and net revenue, surgical cases, clinic visits, ranking of the pediatric surgery residency, publications, grant support, and development and endowment funds. Overall, clinical revenue increased over the period of 5 years, surgical cases and clinic visits increased, and additional facility were hired to more than double the number of physicians. Additionally, faculty and resident satisfaction increased due to the improved clinical working model.

For pediatric patients, care and referrals in the United States are highly complicated by the lack of insurance for pediatric patients. Therefore, state and local social work agency administrations must coordinate funding mechanisms and these must be put into place prior to any care delivery can occur. As a leader in pediatric specialty care since the 1800s, the Johns Hopkins Medical Center set about trying to determine the referral patterns and obstacles inherent in pediatric primary care referral to specialists (Forrest et al. 1999). Their study demonstrated that most pediatricians typically referred patients for assistance in diagnosing a particular sign or symptom and were less likely to do so unless the parents specifically requested a secondary referral or opinion during a telephone call. Referrals to outside specialists dramatically increased if it would likely lead to a surgical or procedural intervention.

Linking pediatric patients to specific care has been a major area of focus for the last two decades. While multiple strategies are being tested by pediatricians and others working in child health, to date there has been no study with a primary focus on how pediatric practices link young children and their families to services and support systems. Vertically and horizontally integrated medical systems must be able to coordinate all major components of care; this holds the greatest promise in ameliorating pediatric linkage deficits particularly for the pediatric congenital population (Mehrotra et al. 2011). Coordination would maximize utilization of co-location, co-management, and networking/information sharing—these would help use existing resources more effectively and improve the quality of care by reducing barriers to care; promoting early referral, linkage, and follow-up; promoting cross-discipline problem-solving and family-centered care; and reducing duplication and fragmentation of services. Service provider networking and information sharing can help uncover gaps in services and can also set the stage for collaborative efforts to address gaps (e.g., coalitions to change policies and programs). Initiating and maintaining regular, multi-sector, or multiagency service provider networking sessions generally exceed the capacity of individual pediatric practices, requiring commitment and funding from others in the community or beyond (Fig. 1).

The referral of pediatric patients to highly specialized centers providing cardiac and congenital evaluation and treatment poses a major barrier for patients being initially seen in freestanding clinics or community practices. Very few centers are capable of providing the high level of care necessary to manage complex pediatric issues. Additionally, a referral for consultation may involve coordination with specialists who are not geographically nearby, and the patient must have the ability to bypass multiple obstacles (i.e. logistical coordination, cost).

Additional barriers to care have been identified and pertain to the psychosocial milieu surrounding every individual patient. Both parents and patients may have an emotional attachment to the physician and provider team involved with treatment of the primary congenital disease(s). There is also physician/provider attachment to patient which may delay or inhibit referral to other specialists as the pediatric patient ages into adulthood. Patients may also have unstable social situations that further complicate future evaluations and referrals.

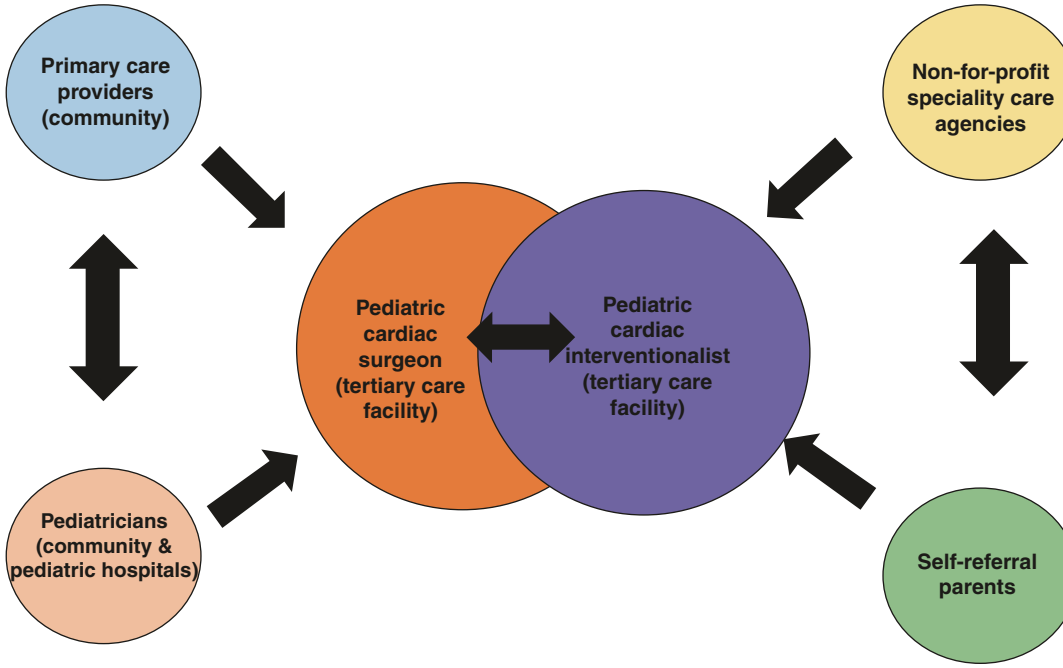

Fig. 1 Venn diagram demonstrating the multi-faceted flow patterns for referral and evaluation of pediatric and congenital heart patients

Evaluation Coordination

Centers providing evaluation and treatment of pediatric cardiac and congenital issues must at a minimum possess a wide array of resources involving technological investments and a broad group of highly specialized personnel. Some of the referral tools are based upon marketing in a geographic catchment area. Pediatricians and parents may learn about particular services through media outlets such as television, radio, and print advertisements. While media outlets are helpful, they do not allow for differentiation of the end-product (high-quality care) and the equitable dissemination of resources being made available to all needy parties.

In the US marketplace, almost every major city has a children's hospital that typically mounts media campaigns to promote the availability of particular medical service resources. Additionally, pediatricians may oftentimes meet pediatric specialists at continuing medical education events in their local community; these are designed to expose primary care providers to new service lines and highly trained pediatric specialists in their community. Otherwise, pediatricians and patients living in less urban or more rural areas face increased barriers to entry for proper care.

Focus-specific care groups, such as the Pediatric Congenital Heart Association (PCHA), provide large platforms to distribute information to both healthcare providers and patients directly. Groups such as PCHA possess the ability to reach large populations of patients through coordinated communication systems. Unfortunately, in the United States, rapid coordination and referral to an appropriate congenital pediatric specialist remain a byzantine process that delays evaluation and care. Standardization of such training via aligned American Board of Pediatrics and American Board of Internal Medicine collaboration toward adults with CHD subspecialty board certification is underway. In addition, numerous task forces have been established to develop strategies to improve access to specialized adult CHD care in collaboration with primary care teams.

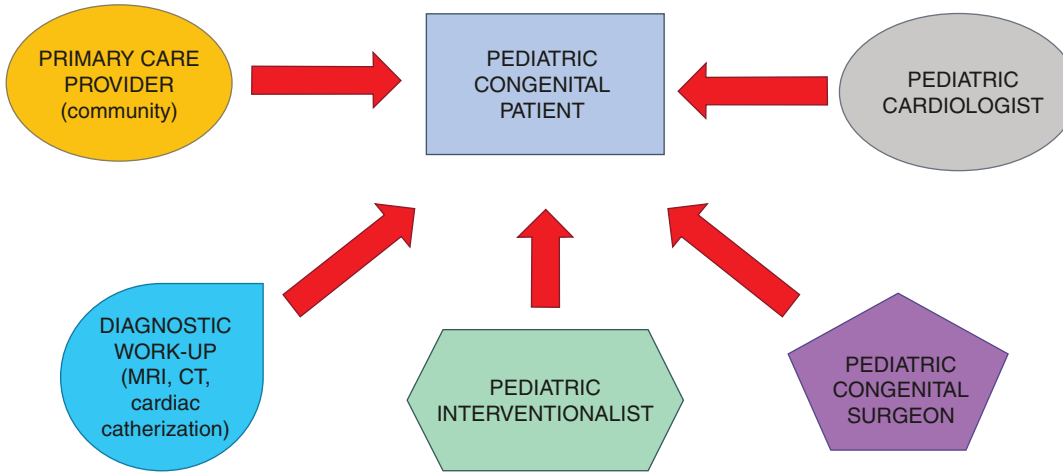

Fig. 2 Venn diagram displaying primary and secondary referral sources contributing to full evaluation of pediatric and congenital patients

Optimal and highly organized care would allow initial evaluation with multiple specialists all in one centralized setting. The advantage of this "setup" is that the evaluation team members can confer with one another and provide a higher level of assessment during one single encounter with the patient and family members (Fig. 2). After the initial assessment has been completed, additional diagnostic testing can be coordinated during a follow-up visit. Again, it is advantageous to schedule the follow-up testing on a single day or sequential days to minimize the disruption to the patient and family while also yielding a short period of evaluation and assessment so that interventions can be planned if necessary.

Surgical and Cardiologic Interventional Issues

Team Structure

The formation of team structure within a medical institution or health care system in order to provide services and treatment interventions for the adult and pediatric patient undergoing congenital surgery is a large undertaking. The medical facility must meet an array of minimum threshold standards pertaining to nursing requirements, physician training requirements, technologic equipment inspection, and local/state inspection for provision of specific services.

Nursing personnel must meet advanced educational and levels of experience commensurate with care of complex pediatric patients. Additionally, nursing personnel must have had previous experience in an intensive care unit or surgical setting with particular exposure to neonates, infants, and children. Physician personnel from the fields of anesthesiology, critical care, cardiology, surgery, radiology, and imaging must all possess the requisite training for their respective fields and be board certified in order to manage a wide range of pediatric anomalies; subspecialty experience/training/certification is also highly recommended. Some states in the United States require a minimum number of cases be performed annually at centers so that a baseline level of proficiency within the institution is maintained. Additionally, training programs must be accredited by the national oversight and reviewing organizations (i.e., American Council for Graduate Medical Education) for each specialty. It is beyond the scope of this chapter to recommend or outline specific requirements as those may vary by state, country, and/or locale in the United States, Europe, and Asia.

Pediatric Surgeon Versus Adult Surgeon

Traditionally, the definition of pediatric patients has been those whom are under the age of 18 years. Therefore, medical and surgical care was confined to pediatric medical centers. However, currently there has been an increase in the number of pediatric patients living into adulthood, and those patients may require additional interventional or surgical congenital procedures past the age of 18. In the United States, there is some controversy as to whether the patient should continue to be treated at a children's hospital versus an adult hospital that may or may not provide pediatric services. Debate continues with regard to optimal location of adult-aged care for patients with congenital or pediatric onset disease. Caring for such adult survivors has generally seemed to be more expensive in pediatric hospitals (Okumura et al. 2006). In 2009, a group of researchers set about to explore the risk factors and outcomes regarding adult patients undergoing congenital surgery in an adult hospital versus a children's hospital (Kogon et al. 2009). The researchers determined that congenital heart surgery can be performed in adults with reasonable morbidity and mortality. Caring for an anticipated aging adult congenital population with increasingly numerous coexisting medical problems and risk factors is best facilitated in an adult hospital setting. Also, when surgery becomes necessary, these adult patients are best served by a congenital heart surgeon. However, recent disease-specific evidence has suggested that adult CHD surgery in pediatric as opposed to adult hospitals might not be associated with an increase in resource use (Kim et al. 2011).

Another study evaluated the same issue and determined that pediatric patients within specific diagnostic groups are more likely to undergo operation by pediatric heart surgeons (PHS), whereas adult patients with congenital heart disease patients within the same diagnostic groups are more likely to undergo operation by non-PHSs. In-hospital death rates are lower for adult congenital heart patients operated on by PHSs. Therefore, adult patients with congenital heart disease should be only analyzed whether or not the primary surgeon was pediatric trained versus non-pediatric trained, and it did not analyze location in an adult hospital versus a children's hospital.

Quality Assurance

Regardless of location, quality assurance and performance improvement measures should be defined so that monitoring of care delivered can be assessed. Outcomes are an important measure of quality, and issues related to poor outcomes should be addressed via a multi-disciplinary team approach. Additionally, participation in a large database submission site (i.e., Society of Thoracic Surgeons—STS) is encouraged so that further knowledge can be obtained from aggregated multiple institutional experience. The STS database offers specific site for congenital heart surgery (http://www.sts.org/national-database/database-managers/congenital-heart-surgery-databas).

"Hybrid" Suites

Medical facilities in the United States offering interventions and surgery for congenital heart surgery have now migrated to a "hybridized" environment that blends components from traditional operating rooms with those of cardiac interventional suites (see Fig. 3). The "hybrid" environments include an array of personnel from both sectors and heavily rely upon the ability to provide fluoroscopic imaging throughout the procedure along with technical specialists to offer potential use of cardiopulmonary bypass and/or assist devices.

The "hybrid" suites may contain a patient table that is compatible with imaging requirements while also containing a mobile fluoroscopic device (i.e., C-arms). Advanced hybrid suites may also contain magnetic resonance imaging and/or computed tomography capability. Additionally, the hybrid rooms have anesthesia machines and large monitors to allow monitoring from all personnel during the procedure.

Fig. 3 Two types of "hybrid" suite with imaging compatible table, mobile fluoroscopic C-arm, large monitors, and anesthesia machine. (Note: Cardiopulmonary bypass unit is not pictured, but should be readily available)

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Electrophysiology in Patients with Congenital Heart Disease

Sophia P. Poorsattar, Jeremy P. Moore, and Komal Patel

Abstract

Cardiac arrhythmias are among the most prominent source of morbidity, impaired quality of life, and mortality in patients with congenital heart disease (CHD). Rhythm disorders encountered in CHD patients span the entire spectrum of brady- and tachyarrhythmias while also ranging in symptomatology and clinical significance. Accordingly, many of these patients require diagnostic or therapeutic interventions in an electrophysiology laboratory. This chapter will discuss the mechanisms behind various arrhythmias, specific procedures performed for diagnosis and treatment, and procedural specific considerations specific to patients with CHD.

Keywords

Ablation · Arrhythmia · Conduction Defibrillator · Electrophysiology · Pacemaker

Introduction

Cardiac arrhythmias are among the most prominent source of morbidity, impaired quality of life, and mortality in patients with congenital heart disease (CHD) (Walsh and Cecchin 2007). This is especially true for patients who underwent surgical correction or palliation at a young age, only to present at a later date with an arrhythmogenic myocardium caused by their inherently atypical anatomy, surgical scars, and chronically remodeled heart after years of suboptimal hemodynamics. Rhythm disorders encountered in CHD patients span the entire spectrum of brady- and tachyarrhythmias while also ranging in symptomatology and clinical significance. While certain arrhythmias may be non-disruptive or benign, others may be poorly tolerated or life-threatening. As such, many of these patients require diagnostic or therapeutic interventions in an electrophysiology laboratory. An understanding of the mechanisms behind various arrhythmias, specific procedures performed for diagnosis and treatment, and procedural specific considerations will help to ensure safe and optimal anesthetic care for this unique patient population.

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The types of procedures that patients present for in the electrophysiology laboratory can be broadly divided into two basic categories: (1) electrophysiology study (EPS) and catheter ablation and (2) cardiac implantable electronic device (CIED) procedures.

Electrophysiology Study and Catheter Ablation in CHD

The spectrum of arrhythmias seen in the CHD population varies according to the underlying anatomical defect and the method of surgical repair or palliation. Arrhythmia pathophysiology is multifactorial and influenced by intrinsic cardiac anatomy, structural remodeling in the setting of abnormal pressure and volume loads, cellular injury and dysfunction related to low perfusion or hypoxic states, and tissue trauma and fibrosis at the sites of surgical interventions (Walsh 2007). With the wide-ranging types of anatomical defects and methods of surgical repairs or palliations, arrhythmias seen in the CHD population span the entire spectrum of tachyarrhythmias. While the preferred treatment options for certain rhythm disorders are pharmacologic or device therapy, for many tachyarrhythmias, EPS and catheter ablation are preferred. The most common indication for catheter ablation in the CHD population is recurrent supraventricular tachycardia, especially intra-atrial reentrant tachycardia (IART).

Atrial and Supraventricular Tachyarrhythmias

IART, which involves a macroreentrant circuit through abnormal atrial myocardium, is the most common arrhythmia mechanism in CHD patients. While IART can develop in the setting of nearly any congenital lesion, it is seen in up to 50% of patients with prior Fontan palliations and in approximately 30% of patients with prior Mustard or Senning operation (Walsh 2007). Fibrous tissue formation from surgical scarring, suture lines, or baffle insertion leads to the discontinuity of atrial muscle bundles and central obstacles for the development of reentrant circuits via anisotropic conduction. With atrial rates of 150–250 beats per min, 1:1 conduction can result in marked hemodynamic compromise or even complete circulatory collapse and are associated with a twofold increased risk for mortality (Khairy et al. 2014). As antiarrhythmic drug therapy is associated with poor long-term success in this condition, treatment has largely shifted to interventional procedures with acute ablation success achieved in 98% of patients (Moore et al. 2021).

As seen in those with typical anatomy, atrial fibrillation can develop in CHD patients that have conditions which result in marked dilation of the left atrium, such as in those with unrepaired atrial septal defects, left-sided valvular disease, and systemic ventricular dysfunction. While trials of cardioversion and pharmacologic rhythm control are often attempted first, catheter-based pulmonary vein isolation and rarely atrioventricular (AV) nodal ablations are alternative treatment options to surgical Maze procedures (Liang et al. 2019).

Accessory AV pathways, resulting in orthodromic AV reentrant tachycardia and AV nodal reentrant tachycardia, involve pathways that bypass or involve (in the case of AVNRT) the normal AV conduction pathway to connect the atrium and ventricle. In this case of antegradely conducting accessory pathways, this may lead to ventricular preexcitation, placing these patients at elevated risk for sudden cardiac death. Accessory pathways are found in a higher proportion of CHD patients with Ebstein's anomaly and levo-transposition of the great arteries (TGA) in which an Ebstein-like malformation exists suggesting a link between the AV valvular deformity and this conduction disturbance (Walsh 2007). In light of this well-appreciated association, catheter ablation has become the preferred treatment of this condition in those with symptomatic SVT or manifest preexcitation (i.e., Wolff Parkinson White pattern). For Ebstein's anomaly in particular, preoperative assessment of accessory pathways is often performed regardless of the symptoms or ECG findings, given the

high prevalence of occult arrhythmogenic substrate (Shivapour et al. 2014). However, mapping and ablative challenges exist in many patients due to displacement of the tricuspid valve hinge-point that occurs along with atrialization of the right ventricle in Ebstein's anomaly repair. As such, rates for ablation success and lack of arrhythmia recurrence for patients with Ebstein's anomaly are lower than in the general population (Khairy et al. 2014).

Guidelines described by the Pediatric and Congenital Electrophysiology Society (PACES) in conjunction with the Heart Rhythm Society (HRS) state that for atrial tachyarrhythmias in adults with CHD, catheter ablation is a Class I recommendation in those with recurrent symptomatic and/or drug-refractory IART or focal atrial tachycardia, those with recurrent symptomatic and/or drug-refractory supraventricular tachycardia related to accessory AV connections or twin AV nodes, and those with ventricular pre-excitation and high-risk or multiple accessory pathways. For patients with symptomatic drug-refractory atrial fibrillation, catheter-based ablation is a Class II recommendation (Khairy et al. 2014).

Ventricular Tachycardias

While ventricular ectopy and non-sustained ventricular tachycardia are common, sustained ventricular tachycardia is rare, occurring in only 0.1–0.2% of adults with CHD (Gallego et al. 2012). Of the CHD lesions, sustained monomorphic ventricular tachycardia occurs most commonly in tetralogy of Fallot where the right ventricular outflow tract is markedly scarred post-surgical intervention (Khairy et al. 2014). While sustained ventricular tachycardia is associated with well-described isthmuses for catheter mapping and ablation (Zeppenfeld et al. 2007; Moore et al. 2013), recurrence is possible even after acute ablation success. Currently, there is lack of consensus as to whether ICD implantation is required despite successful catheter ablation of monomorphic VT in the setting of tetralogy of Fallot and this is an area of active investigation. Such consideration should be made carefully and in the context of follow-up EPS to document non-inducibility after successful catheter ablation.

Society guidelines for catheter ablation of ventricular arrhythmias in adults with CHD provide a Class I recommendation for its use as an adjunctive therapy to ICD in those with recurrent monomorphic ventricular tachycardia, ventricular tachycardia storm, or multiple appropriate shocks that are not manageable by drug therapy or device reprogramming. Catheter ablation is a Class II recommendation in those with select ventricular tachycardias with high-risk features such as poor hemodynamic tolerance, deteriorating ventricular function, or as an alternative to adjunct drug therapy (Khairy et al. 2014).

Procedural Considerations

Transvenous EPS dates back to 1971 in which the first simultaneous electrical stimulations with recordings of intracardiac signals were performed (Wellens et al. 1972). Over time, advancements in EPS have allowed detecting tachyarrhythmia mechanisms and the localization of arrhythmogenic foci with improved precision with interventional catheter-based ablation techniques for the treatment of tachyarrhythmias emerging soon after. This improved understanding of rhythm abnormalities has proven especially useful when diagnosing and treating the complex rhythm disorders seen in the CHD population.

Electrophysiology studies and catheter ablation for patients with CHD must be performed in dedicated electrophysiology laboratories where procedural specific equipment is readily available. This includes external defibrillation capability, biplane fluoroscopy, an electrocardiographic and intracardiac electrogram recording system, an electroanatomic ("3D") mapping system, and readily available access to real-time laboratory assessment. Access to remote magnetic navigation (RMN) may serve as an additional resource in some situations. Due to their complex anatomy and physiology,

the American Heart Association/American College of Cardiology recommend that these procedures be performed by electrophysiologists with expertise in the management of adult CHD (Stout et al. 2019). Similarly, it is advisable that these procedures be performed at specialized centers with anesthesiologists and cardiac surgeons with an expertise in the care of adult CHD patients (Finnerty and Griffin 2021). In patients with CHD necessitating structural intervention, there has also been an emergence of specialized centers performing concomitant electrophysiologic and structural interventions with favorable outcomes (Lindsay et al. 2018).

While the femoral vein is the most common choice for venous access, alternative approaches may be required based on patient anatomy, including subclavian, internal jugular, or transhepatic (e.g., with interrupted IVC or femoral venous occlusions). If the procedure requires entry into the left side of the heart, the approach is generally transseptal, transbaffle/transconduit (Moore et al. 2020), or even transpulmonary (Moore et al. 2016a). Less commonly, a retrograde aortic approach is utilized (especially when using RMN).

Once access is obtained, various mapping techniques can be utilized to identify sites for catheter ablation. For organized and hemodynamically tolerated tachyarrhythmias, three-dimensional electroanatomic mapping is generally performed first to delineate the key components of (or even the entire) reentrant circuit. The map is then evaluated to determine the optimal catheter ablation site that is critical to tachycardia maintenance (Fig. 1). When choosing the optimal ablation target, care is required to avoid potential collateral damage to structures, such as the phrenic nerve, sinus or AV node, or coronary arteries. Prior to catheter ablation energy delivery, entrainment is typically performed at the potential target site to verify critical participation in the reentrant circuit.

The use of three-dimensional (3D) mapping systems has allowed for improved mapping and ablation success in the complex targets observed in CHD. Electroanatomic mapping systems allow for a 3D reconstruction of electrograms and chamber geometry. Visually, this takes the form of color-coded static maps depicting isochrones of electrical activity merged with cardiac reconstructions from magnetic resonance or computed tomography imaging obtained prior to the procedure (Walsh 2007; Chua et al. 2012). Recognizing the improved success with this mapping technique, society guidelines recommend that EPS for adults with CHD be performed at facilities with this technology available (Khairy et al. 2014; Stout et al. 2019).

Upon identification of the critical isthmus of the reentrant circuit, catheter ablation is performed to render it electrically inert via either irrigated radiofrequency (burning) or cryothermal (freezing) energy (Chua et al. 2012). With radio frequency catheter ablation (RFA), the catheter tips produce high tissue temperature through resistive (and to a lesser extent, conductive) heating to disrupt the tissue and create electrical scar. In cases where proximity to the AV conduction system is expected ("peri-nodal substrates"), cryoablation may be the preferred energy source over radiofrequency energy in CHD (Khairy et al. 2014).

Anesthetic preparation for EPS and catheter ablation starts with a pre-anesthesia assessment, which should include the arrhythmia to be addressed, the patient's anatomy and cardiovascular reserve, and the anticipated procedural approach including if a concomitant procedure is to be performed. The choice of anesthetic technique is partly dictated by patient comorbidities, length of procedure, and anticipated complications. In those with limited cardiopulmonary reserve, vasoactive support, advanced hemodynamic monitoring, controlled ventilation, and frequent lab checks may be required. With technically challenging cases, procedural times can exceed 4 h in duration during which the patient is expected to lay flat and remain motionless to facilitate accurate mapping and ablation. Placement of foley catheter should be considered for these prolonged complex procedures.

The type of ablation procedure also influences anesthetic management. In patients undergoing supraventricular or ventricular tachycardia ablation, a light sedation technique may be preferred

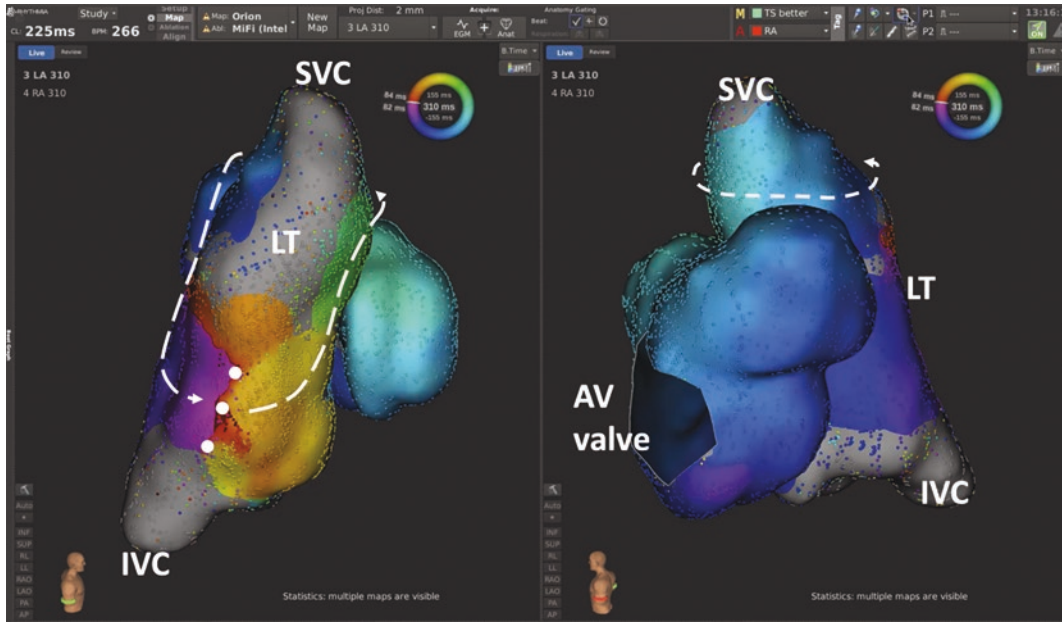

Fig. 1 Example of a three-dimensional electroanatomical map in a patient with recurrent intra-atrial reentrant tachycardia after lateral tunnel Fontan operation (right and left lateral views are shown). There is a macroreentrant circuit (atrial rate 190 beats per min; dashed white arrows) that rotates around a combined obstacle incorporating the SVC and morphological right atrial atriotomy. The circuit was successfully interrupted with irrigated radiofrequency energy applied to the isthmus between the lower end of the atriotomy incision and the IVC (solid white circles). *AV* atrioventricular, *LT* lateral tunnel, *IVC* inferior vena cava, *SVC* superior vena cava

to avoid suppression of the ventricular arrhythmia. In patients undergoing atrial fibrillation or atrial flutter ablation, a transesophageal echocardiogram may be required to rule out intracardiac thrombus prior to proceeding with the case. In atrial fibrillation ablations, a general anesthetic technique is performed with placement of an orogastric tube and esophageal temperature probe for reducing the rare but possibly fatal complication of atrio-esophageal fistula formation. Additionally, neuromuscular blockade is avoided to allow for recognition of phrenic nerve stimulation from the ablation catheter when targeting either the right sided pulmonary veins or posterolateral right atrium. With transseptal puncture for any ablation procedure, systemic heparinization is required to reduce the risk of thromboembolism. Caution must be taken with fluid management as the electrophysiologist may use 2–3 L of crystalloid while irrigating the ablation catheters or a transseptal sheath throughout the case. During mapping, the patient may experience frequent rhythm changes, which may result in hemodynamic instability and necessitate cardioversion or defibrillation. In the event of inadvertent cardiac perforation and pericardial tamponade, the electrophysiologist may have to place a pericardial drain. With local anesthetic infiltration at the cannulation sites, postoperative pain is usually minimal and is effectively managed with intravenous or oral analgesics as needed. Disposition to the postanesthetic care unit or intensive care unit depends on the patient's hemodynamic condition and the complexity of the procedure.

Cardiac Implantable Electronic Devices

CIEDs fall into two principal categories, implantable cardioverter-defibrillators (ICDs), which are for the prevention of sudden cardiac death (SCD), and pacemakers, which are for the treatment of symptomatic bradycardia.

Implantable Cardioverter-Defibrillators

Sudden cardiac death is responsible for 20–25% of all-cause mortality in adults with CHD with the majority of causes being of arrhythmogenic etiology (73–80%) (Khairy et al. 2014). The congenital lesions identified to be highest risk for the development of SCD include tetralogy of Fallot, TGA (both dextro- and levo-variations), Ebstein's anomaly, left-sided obstructive lesions, and Eisenmenger syndrome (Silka et al. 1998; Koyak et al. 2012).

ICDs are placed for the primary or secondary prevention of SCD. As described in the 2014 PACES/HRS guidelines, Class I indications for the primary prevention of adults with CHD include those who meet standard recognized criteria (biventricular physiology with a left ventricular ejection fraction of ≤35% and advanced heart failure symptoms) as well as those with spontaneous sustained ventricular tachycardia. ICD therapy is also recommended to be considered in those with tetralogy of Fallot with high-risk features for SCD, cardiomyopathies or univentricular hearts with high-risk features for SCD, and syncope of unknown origin with known or suspected history of ventricular arrhythmia. As expected, ICD therapy for secondary prevention in those with a history of life-threatening arrhythmia is a Class I indication for adults with CHD (Khairy et al. 2014).

Traditional transvenous ICD (TV-ICD) placement mirrors that of transvenous permanent pacemakers (TV-PPM) with the subcutaneous or submuscular insertion of a pulse generator, normally in the left infraclavicular area, and leads that are affixed to the endocardium via a transvenous route, typically the subclavian vein. Among all patients, early complications of TV-ICD placement include vascular injury, pneumothorax, hemothorax, cardiac perforation, pericardial effusion, and tamponade. Late complications include lead failure and lead-related infective endocarditis (Bowman et al. 2021). Compared to the general population, TV-ICDs present many challenges in the adult CHD population as these patients often have complex central venous anatomy that is not amenable or potentially hazardous to device placement, such as venous anomalies, intracardiac shunts, Fontan anatomy, or mechanical right AV valves (Khairy et al. 2006). As an alternative to transvenous lead implantation, subcutaneous ICDs or an epicardial approach may be considered in these situations (also discussed below with pacemakers).

Due to the increased or prohibitive risk of TV-ICD placement in certain adults with CHD, novel configurations of ICD therapy have been developed. One such configuration is the subcutaneous ICD (S-ICD), which gained Federal Drug Administration (FDA) approval in 2012. Like a TV-ICD, a S-ICD consists of a generator and a shocking lead. With the S-ICD, however, the generator is inserted subcutaneously in the anterolateral position while the shocking lead is tunneled midline and with the coil oriented vertically in the left or right parasternal position (Fig. 2a, b). For adult CHD patients, S-ICDs offer many advantages. First, the superficial position outside of the thoracic cavity means vascular access is not required. This provides an attractive ICD therapy option in patients with no venous access, acquired stenosis or obstruction of central veins, awaiting heart transplantation, or prior and/or at risk for endovascular lead infection (De Maria et al. 2015). Further, in patients who have device failure or young patients who necessitate multiple device revisions throughout their lifetime, complications related to repeated transvenous lead additions or extractions are avoided (Brunner et al. 2014). Accordingly, S-ICD use is recommended for adult CHD patients when feasible (Al-Khatib et al. 2018; De Maria et al. 2014). Certainly, without endomyocardial lead insertion, limitations exist. S-ICDs have no pacing capabilities (aside from short-term post-shock back up pacing), a larger generator, a shorter battery life, and a prolonged time to therapy as compared to TV-ICDs. Additionally, certain patients may not be a suitable candidate for S-ICDs due to inadequate sensing of subcutaneous signals (such as patients with heavy weight, hypertrophic cardiomyopathy, prolonged QRS interval, or inappropriate R to T wave ratio) or anatomic characteristics that increase complication risk (such as insufficient subcutaneous tissue or chest wall abnormalities) (De Maria et al.

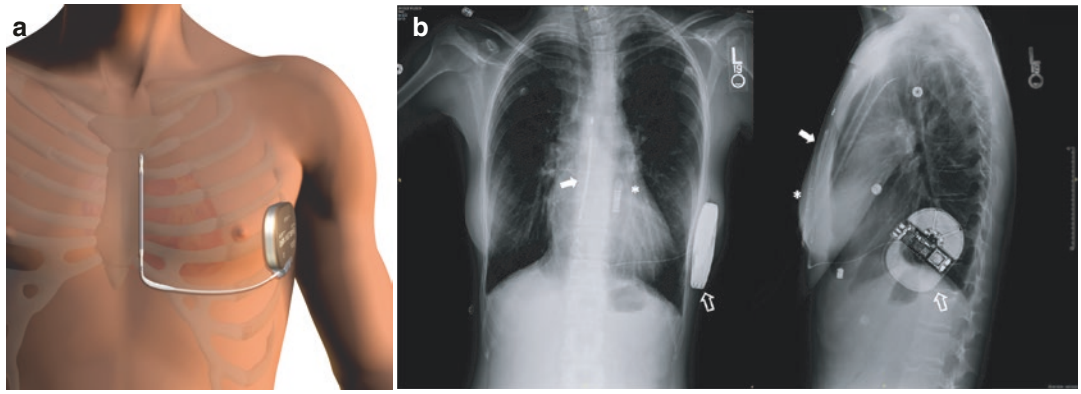

Fig. 2 (**a**) Schematic presentation of the of the anatomical placement of the Emblem™ Subcutaneous Implantable Defibrillator (S-ICD). (© 2020 Boston Scientific Corporation or its affiliates. All rights reserved. Used with permission from Boston Scientific Corporation). (**b**) Posterior-anterior and lateral chest x-ray after S-ICD placement in a woman with Eisenmenger syndrome and documented VT. The pulse generator has been placed in a left axillary position across from the apex of the heart (open arrowhead) with the subcutaneous shocking coil tunneled over the sternum (solid arrowhead). A prior implantable loop recorder is shown in a parasternal position (asterisk). Given the patient's congenital physiology, the patient underwent preoperative truncal plane block to limit the need for general anesthetic

2015). The safety and efficacy of the SICD in the CHD population has been previously described (Moore et al. 2016b).

Anesthetic considerations for TV-ICD placement mirror those of the considerations for TV-PPM implantation (also discussed below). For S-ICD placement, the decision for general versus sedation technique and types of monitoring depends on individual patient factors. The patient is positioned supine with the left arm abducted in order to facilitate exposure of the left axilla and chest wall. If performed under sedation rather than general anesthesia, adequate analgesia may be challenging with local lidocaine infiltration alone as the sizable generator box is inserted in an intramuscular position between the serratus anterior and the latissimus dorsi muscle and the lead tunneled through substantial subcutaneous tissue to reach its final parasternal position. To obviate the need of supplemental analgesics, regional blockade with a serratus anterior plane block may be effective for analgesia in the T2–T9 dermatomal distribution through blockage of the lateral cutaneous intercostal nerves (Droghetti et al. 2018). Once the device is inserted, one or more defibrillation threshold tests will be performed. This energy delivery may be quite unpleasant for an awake or minimally sedated patient, and a short-acting anesthetic agent is recommended at this point for patient comfort. As an energy delivery may lead to hemodynamic instability, in high-risk patients, this test may be avoided (Finnerty and Griffin 2021).

Pacemakers

Permanent pacing is often required in patients with CHD for bradyarrhythmias either due to a diseased conduction system (whether inherent to the anatomic substrate at birth or with progressive deterioration over time) or conduction system injury secondary to surgical or procedural interventions. Progressive, spontaneous AV block, for instance, is classically seen with levo-TGA, where the incidence approaches 2% per year postnatally (Graham et al. 2000; Beauchesne et al. 2002). The PACES/HRS guidelines describe the Class I recommendations for permanent pacing in adults with CHD to include those with symptomatic bradycardia from sinus node dysfunction or any degree of AV block, congenital complete AV block with ventricular conduction or function abnormalities, and post-operative high-grade second- or third-degree AV block that is not expected to resolve. Additional Class II indications include adults with CHD with vary-

ing degrees of sinus node or AV conduction disturbance with concerning features and for those with a high proclivity for developing IART (Khairy et al. 2014).

The two most common configurations for permanent pacemaker placement are transvenous or epicardial systems. Transvenous systems account for the majority of implants, while epicardial systems are reserved for patients not amenable to transvenous implantation. As mentioned previously, with TV-PPM placement, a pulse generator is typically placed in the left upper pectoral region with leads advanced to the endocardium via a transvenous route. With epicardial pacemaker implantation, surgical exposure of the heart is required. The choice of optimal generator position and route depends on various patient-specific factors.

The challenges of TV-PPM placement in the adult CHD population mirror those of TV-ICDs. Additionally, TV-PPMs are fraught with similar early and late complications related to the leads, generator pocket, and patient anatomy. To circumvent these issues, leadless pacemakers were developed, which combine a pacing lead and generator into one small device that inserts into the right ventricular septum via a transvenous approach (Fig. 3a, b). While two leadless pacemakers exist, Nanostim™ (St Jude Medical, Sylmar, CA, USA) and Micra™ (Medtronic, Minneapolis, MN, USA), presently, only the Micra™ is commercially available. In its current form, the device is only suitable in patients who require single right ventricular chamber pacing. While this includes a smaller pool of suitable candidates than TV-PPMs, leadless pacemakers are an attractive alternative in adult CHD patients with poor venous access in the upper body in whom permanent transvenous leads would be unfavorable. Further, at end of life, these devices offer the option of either endovascular device retrieval (if recently implanted) or abandonment with implantation of additional devices simultaneously without significant hemodynamic compromise (Finnerty and Griffin 2021). As the technology is relatively new, long-term durability and outcome data remain unknown; however, early complication rates are comparable to those seen with traditional TV-PPM (4.8% and 4.1%, respectively) (Tjong and Reddy 2017).

Anesthetic preparation for pacemaker placement starts with a pre-anesthesia assessment,

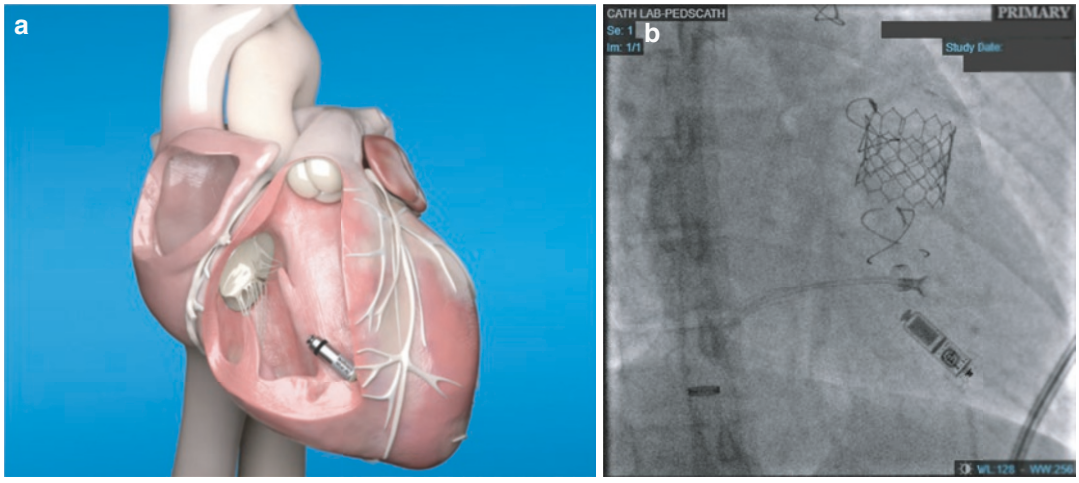

Fig. 3 (**a**) Schematic presentation of the anatomical placement of the Micra™ Transcatheter Pacing System. (Image courtesy of Medtronic). (**b**) Fluoroscopy during deployment of a leadless transcatheter pacemaker in a young woman with tetralogy of Fallot and intermittent episodes of bradycardia. The delivery system is shown in the body of the right ventricle with the pacemaker recently deployed at the septal right ventricular apex. The delivery sheath can be seen at the junction of the right atrium and the inferior vena cava. A transcatheter valve had been placed in the pulmonary position at the same procedure prior to transcatheter pacemaker placement in order to treat pulmonary stenosis

which should include an accurate understanding of the indication for pacemaker placement, the patient's anatomy and cardiovascular reserve, and the anticipated procedural approach. For TV-PPM, placement of a left upper extremity peripheral intravenous line allows for a venogram to be performed prior to incision. While important for all patients undergoing TV-PPM placement, this is especially pertinent in CHD patients with numerous congenital and post-surgical structural variances to confirm venous anatomy and patency. The choice of anesthetic technique and advanced monitoring are dictated by patient comorbidities. In the absence of contraindications, sedation with local topicalization in the area of the generator pocket and venous exposure is often well tolerated as this is most stimulating part of the procedure (Chua et al. 2012). With implantation of right atrial and coronary sinus leads, phrenic nerve capture is assessed and paralytics should be avoided. Using a sedation technique with oxygen administration via nasal cannula or face mask, precautions must be taken to reduce the risk of airway fire as the generator pocket is often implanted in the upper chest in close proximity to the airway with the use of electrocautery. To prevent oxygen accumulation under the sterile drape, an oxygen-air blender that can deliver a low concentration of oxygen and a supportive bar that can lift and secure the drape away from the face should be utilized. For leadless pacemaker implantation, venous access is normally percutaneously via the femoral vein. In contrast to TV-PPM placement, no chest wall dissection is required making the procedure much less stimulating and tolerable for most patients with minimal sedation and local anesthesia alone.

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Cardiopulmonary Bypass in Children and Infants

Filip De Somer

Abstract

Surgical correction of congenital heart disease with cardiopulmonary bypass remains a challenge. Conduct and components of the cardiopulmonary bypass are important as they can attenuate peri- and postoperative morbidity. This chapter will discuss the different components of cardiopulmonary bypass as well as the impact of cardiopulmonary bypass on systemic inflammation and coagulation.

Keywords

Cardiopulmonary bypass · Pump · Cannulas · Host response · Systemic inflammation

Introduction

One of most important medical advances of the twentieth century was cardiac surgery. John Gibbon performed the first successful cardiac operation with cardiopulmonary bypass (CPB) (Edmunds 2003). Initially, the technology was complex and unreliable and was, therefore, slow to develop. The introduction of better and more hemocompatible polymers in combination with better pumps and monitoring has led to extraordinary improvements over the years. These improvements relate not only to equipment but also to a better understanding of the normal and pathological physiology.

Better design and improved conduct of pediatric cardiopulmonary bypass (CPB) are responsible for the fact that complex cardiac anomalies can nowadays corrected earlier in live with low mortality and morbidity. Nevertheless, initiating CPB in a neonate remains a challenge because of child's low blood volume, its often immature organs, and abnormal anatomical structures.

This chapter discusses some of the improvements as well as some of the remaining problems.

Components of CPB

Due to the heterogeneity of the pediatric population and the often abnormal anatomy, there is no such thing as a standard CPB circuit for neonatal and pediatric cardiac surgery. The most challenging components are vascular access, tubing, pump, and oxygenator choice.

Vascular Access

Since the start of CPB in the early 1950s of last century, nonoptimal vascular access was known

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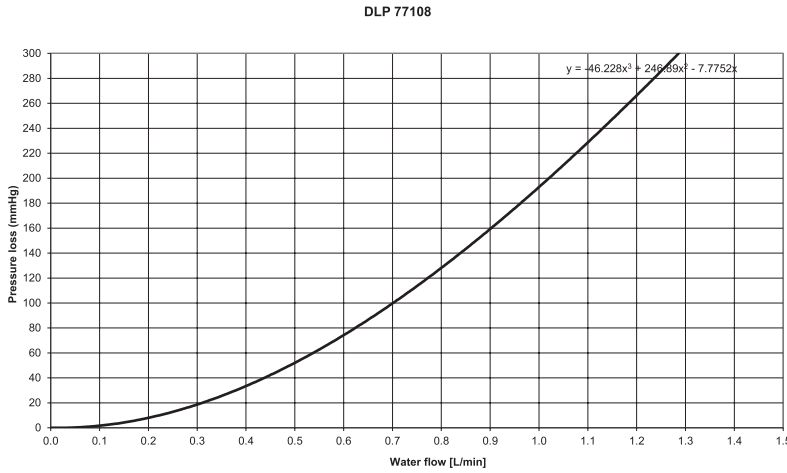
to have a direct impact on the hemodynamic support of a patient. From a physiological and anatomical point of view, the venous and arterial circulations are quite different. The arterial circulation is mainly a high pressure, low compliance system, whereas the venous system is a low pressure, high compliance system. Therefore, problems encountered in obtaining optimal arterial or venous access are different.

Inappropriate sizing of the arterial cannula, bleeding of the cannulation site, and rarer malposition of the cannula are potential problems with arterial cannulation. A too small cannula diameter leads to high shear stress and pressure drop over the cannula tip, which creates hemolysis and activates leukocytes and blood platelets. In addition, the high blood velocity inside the arterial cannula creates a jet inside the aorta causing selective perfusion, while the Venturi effect might steal blood from the brain vessels. On the other hand, a too large cannula will cause partial obstruction of the vessel lumen and increases afterload for the heart during weaning of CPB. High resistance inside the cannula or arterial line is less of a problem as the cannula is located downstream of the arterial blood pump. Many centers determine arterial cannula diameter empirical based upon historical experience. This is because manufacturers in general provide pressure–flow curves using water instead of blood or a blood analog. As water has a lower viscosity than blood, this can lead to major bias, especially in patients with an abnormal hematocrit or patients undergoing hypothermic cardiac surgery. In order to overcome this problem and to have a better estimate of the pressure–flow characteristics of a given cannula, a simple technique has been proposed, which is represented in (Fig. 1) (De Wachter et al. 2002).

Assessing access of the venous side is more complex due to boundary conditions that are more stringent. Venous return toward the heart depends upon the pressure difference between the mean circulatory filling pressure and the pressure in the right atrium. This pressure difference is relatively small, 7 mmHg (Guyton et al. 1954, 1957, 1962), and decreases with increases in right atrial pressure. The smaller the pressure difference, the more it jeopardizes venous drainage.

Venous vascular access connects wide, low-resistance, collapsible blood vessels with smaller diameter, stiff, artificial conduits of known physical characteristics. The smaller diameter of both venous line and venous cannula, compared to the native veins, requires a higher pressure difference than the physiological pressure difference to obtain optimal venous drainage (Galletti and Brecher 1962). The magnitude of that increase in pressure difference for obtaining optimal drainage depends on tubing diameter, tubing length, and blood viscosity (Ni et al. 2001). The latter depends on both hematocrit and temperature. Several methods are available to increase this pressure difference. Creating an additional negative pressure between cannula tip and venous reservoir increases the pressure difference. Placing the venous reservoir lower than the patient thus creating a siphon, due to the hydrostatic column between patient and reservoir, or applying a vacuum source to the venous reservoir are both used to achieve this. The latter has the additional advantages that the venous reservoir can be positioned at the level of the patient what significantly reduces the length of the tubing and that the amount of negative pressure is adaptable. Increasing negative pressure augments venous drainage in a linear manner while resistance remains more or less constant. However, excessive negative pressure is avoided as at a certain point a further increase in negative pressure leads to partial or full collapse of the vein, with no further increase in blood flow and, therefore, resistance will start to increase (Galletti and Brecher 1962). Correct choice of a venous cannula is critical, as it represents the smallest diameter and, thus, the highest resistance. Reducing its diameter by 50% reduces flow to 1/16th of the original flow. In addition, the length of the smallest part of the cannula diameter is important, doubling the length decreases flow by 50%. The high velocity inside the cannula in opposition to the lower velocity in the blood vessel creates a Venturi effect at the cannula tip and its side holes. As such, the ratio between the diameter of the vein and the diameter of the cannula is a point of attention. According to Galetti, this ratio should be around 0.5 in order to

Pressure flow curve (water) Medtronic DLP 77108 (provided by the manufacturer)



We can represent these data by a parabolic fit: $\Delta P_{water} = a \cdot Q_{water}^{2} + b \cdot Q_{water}$ In the example above we obtain: $\Delta P_{water} = 166.98 \cdot Q_{water}^{2} + 23.64 \cdot Q_{water}$

In order to obtain the values for blood with a given hematocrit and temperature we need to rescale the coefficients with ratios of density and dynamic viscosity:

$$a_{blood} = a_{water} \cdot \frac{\rho_{blood}}{\rho_{water}} \qquad b_{blood} = b_{water} \cdot \frac{\mu_{blood}}{\mu_{water}}$$

Calculate density and viscosity for water and blood

$\rho_{water} = 997 \frac{kg}{m^3}$ water density

$\eta_{water} = 0.001 \frac{kg}{m \cdot s}$ water viscosity at 20°C

Blood characteristics during cardiopulmonary bypass

$Hct := 25\%$ Hematocrit [%]

$T_{blood} := 32$ Arterial blood temperature [°C]

$$\rho_{blood} = 1.09 \frac{gm}{cm^3} \cdot Hct + 1.035 \frac{gm}{cm^3} \cdot (1 - Hct)$$

$\rho_{blood} = 1.049 \times 10^3 \frac{kg}{m^3}$ Blood density during CPB

$$\eta_{plasma} = \frac{\exp\left[-5.64 + \frac{1800}{(T_{blood} + 273)}\right]}{100} \cdot poise$$

Fig. 1 Method for conversion of water pressure flow curve into blood pressure flow curve

$$\eta_{blood} = \eta_{plasma} \cdot \exp(2.31 \cdot Hct) \qquad \eta_{blood} = 2.314 \cdot cpoise$$

Calculate ratios

$$\rho_{ratio} = \frac{\rho_{blood}}{\rho_{water}} = 1.052 \qquad \eta_{ratio} = \frac{\eta_{blood}}{\eta_{water}} = 2.314$$

What is the pressure drop over a 77108 DLP cannula during CPB at a blood flow of 0.8 L/min?

$Q := 0.8$ Flow in L/min

$$\Delta P_{water} := 166.98 \cdot Q^2 + 23.64 \cdot Q = 126$$

$$\Delta P_{blood} := 166.98 \cdot \rho_{ratio} \cdot Q^2 + 23.64 \cdot \eta_{ratio} \cdot Q = 156$$

Fig. 1 (continued)

avoid collapse of the vein around the side holes of the cannula (Galletti and Brecher 1962). Finally, also cannula and tip design (De Somer et al. 2002) influence drainage efficiency.

In children, vacuum-assisted venous drainage (VAVD) is becoming more and more the standard. This technique applies vacuum on the venous reservoir in order to increase the pressure differential (Durandy 2009a, b; Durandy and Hulin 2006). Using VAVD to augment venous drainage in case of malposition of one or more venous cannula(s) is avoided. Under such conditions, VAVD increases resistance in the cannula with marginal or no increase in drainage. Subsequently, it generates higher blood velocities over the nonblocked openings of the cannula. Finally, it increases shear stress and leads to an increase in hemolysis. Before applying any form of assisted venous drainage, one should check proper cannula placement. After this check, one can use assisted venous drainage in cases where one wants to reduce priming volume by placing the oxygenator at the same height as the patient or by using a smaller diameter venous line or by combining both strategies (Pappalardo et al. 2007).

Optimal negative venous drainage pressure for VAVD varies between −30 and −80 mmHg depending at which location pressure is measured. It is good practice to measure the negative pressure as it gives an estimate of the pressure at the cannula tip and helps in preventing vein collapse. Vein collapse will occur once the negative pressure at the cannula tip exceeds −4 mmHg. Unfortunately, the pressure at the cannula tip is difficult to obtain in clinical practice so most perfusionists measure the pressure somewhere between the cannula and the reservoir top. As a result, the obtained pressure value is the sum of the resistance in the cannula and the venous line between the measurement point and the cannula tip. The latter might explain the large differences in reported values. Table 1 is an illustration that shows for 3/16 in. tubing and 1/4 in. tubing, the differences in blood velocity and required pressure drop for a required venous drainage of 1 L/min.

In general, assisted venous drainage is helpful in all cases where siphon drainage alone is insufficient due to high resistances in the venous cannula and venous line, in cases where venous pressure remains high despite proper cannula position and in those cases where the operative field is not dry (Murai et al. 2005).

Optimizing arterial and venous vascular access is mandatory, as it determines maximum

Table 1 Fluid dynamical characteristics of venous tubing

Tubing diameter (7.in.)	3/16	1/4
Blood flow (L/min)	1	1
Pressure difference (mmHg)	51	11
Velocity (cm/s)	94	53
Reynolds number	2019	1514
Wall shear stress (dynes/cm^2)	54	15

Data generated with: Hematocrit: 25%; Temperature: 32°C; Tubing length: 150 cm

Table 2 Impact of tubing diameter on fluid dynamics

Tubing diameter (in.)	1/8	3/16	¼	3/8
Volume (mL/m)	8	18	32	71
Pressure difference (mmHg/L)	234	54	15	5
Velocity (cm/s)	210	94	53	23
Reynolds number	3028	2019	1514	1009
Wall shear stress (dynes/cm^2)	247	54	15	6

Data generated with: Hematocrit: 25%; Temperature: 32°C; Tubing length: 150 cm; Blood flow: 1 LPM

blood flow and thus oxygen delivery to the organs. Malposition of an arterial cannula can obstruct cerebral blood supply or cause a preferential flow into the descending aorta leading to an inappropriate oxygen supply to the brain. Alternatively, obstruction of the superior vena cava cannula may decrease cerebral venous drainage and potentially lead to brain dysfunction. Routine monitoring of cerebral oxygenation by near-infrared spectroscopy (NIRS) is a valuable help for early detection of such problems (Gottlieb et al. 2006; Ginther et al. 2011; Redlin et al. 2011).

Tubing

Tubing in the CPB circuit interconnects all main components of the circuit. The most common used polymer is PolyVinyl Chloride (PVC) with exception of the tubing used in the pump boot, which is often silicone. In opposition to PVC, silicone is not temperature sensitive and maintains its diameter and hardness during cooling. Original PVC contained di-(2-ethylhexyl)-phthalate (DEHP) as plasticizer in order to make PVC flexible. Recent concerns with respect to the potential toxicity of DEHP (Greiner et al. 2012) result in the demand of many centers for DEHP-free PVC tubing for their pediatric circuits.

Length and size of the tubing will have a major impact on volume, shear stress, and pressure drop (Table 2), and the clinician will have to make choice based upon the clinical conditions.

Blood Pumps

Pumps classify into two main categories: displacement pumps and rotary pumps. Periodic volumetric changes of a working space characterize energy in displacement pumps. A classic example of a displacement pump is the roller pump. The working principle is that two rollers, placed opposite to another, "roll" the blood through a piece of tubing. In case of completely occlusion of the tubing by the rollers, the pump can generate both positive and negative pressures. Therefore, a roller pump is multifunctional as it is able to pump blood as well as aspirate blood. A roller pump is relatively independent of factors such as resistance and hydrostatic pressure head, encountered in the average CPB circuit. The output of an occlusive roller pump depends upon two main variables: the number of revolutions per min of the pump head and the internal diameter and length of the tubing in the pump head:

$$Q = \pi \cdot \text{radius}^2 \cdot \text{length} \cdot \text{RPM}$$

where RPM is the revolutions per minute.

A disadvantage of roller pumps is spallation (Briceno and Runge 1992; Peek et al. 2000). Due to the continuous compression of the tubing by the roller, the polymer of the tubing starts to weaken and to erode, resulting in generation of small particles (Briceno and Runge 1992; Peek et al. 2000; Kim and Yoon 1998). In order to control spallation, it is advocated to use a

dynamic occlusion setting of the pump rollers (Tamari et al. 1997). As neonatal and pediatric CPB circuits have high resistances due to the small diameter tubing, roller pumps remain the first choice. In larger children or young adults, one might prefer a rotary pump and more specific a centrifugal pump. Centrifugal pumps operate on the principle of moving fluid by creating a pressure gradient between inlet and outlet of the pump. The rotation of the pump rotor creates a vortex responsible for the pressure gradient. The vortex creates an area of low pressure in the center and an area of high pressure on the sides. The resulting rate of blood flow will depend upon the pressure gradient and the resistance at the outlet of the pump. The latter is a function of two variables: the CPB circuit (oxygenator, filter, tubing, and arterial cannula) and the systemic vascular resistance of the patient. A centrifugal pump is a pressure pump because the flow produced by a centrifugal pump directly depends on the pressure that the centrifugal pump rotor generates, which depends on the number of revolutions per minute (RPM) and the rotor design. In contrast to a roller pump, a centrifugal pump is afterload dependent and, thus, susceptible to changes in resistance in both circuit and patient. This affects forward flow and makes it necessary to use a centrifugal pump in conjunction with a flow sensor. Although a centrifugal pump, due to its nonocclusive working principle, has no spallation, high resistances after the pump may lead to high shear stresses and hot spots inside the pump head (Araki et al. 1995a, b; Ganushchak et al. 2006). As a centrifugal pump is nonocclusive, which can lead to back flow when the RPM are set too low. This is in particular important during the start and weaning of the CPB.

Oxygenator

The oxygenator is without doubt the most important component in the CPB circuit. It is not only responsible for exchanging oxygen and carbon dioxide but for the administration of volatile anesthetics. The oxygenator comprises an integrated heat exchanger that allows cooling and warming of the patient. A heat exchanger is indispensable as some extensive repairs may require hypothermia and or deep hypothermic circulatory arrest (DHCA). Most recent oxygenators are available with an integrated filter, thus, avoiding the need for a separate arterial line filter (Ginther et al. 2013; Lin et al. 2012). In pediatric surgery, most centers use an open venous reservoir with integrated cardiotomy. The latter filters and defoams blood aspirated from the surgical field. The main reason for choosing open systems lays in the fact that open systems allow assisted venous drainage, which is helpful in optimizing venous drainage and in reducing priming volume (Durandy 2013, 2015).

Nowadays, extra luminal hollow fiber membrane oxygenators are standard. For neonatal and pediatric usage, several sizes are available. The final decision which to use is usually made based upon priming volume, surface area, rated blood flow, and available connector sizes, all in relation with the size of the patient and the type of surgical repair. Table 3 shows the characteristics of some neonatal and pediatric oxygenators. Originally, the reference flow of a given oxygenator was defined by the Association for the Advancement of Medical Instrumentation (AAMI) as the flow rate at which normothermic whole blood having a hemoglobin content of 120 g/L, a base excess of 0, and a venous saturation of 65% increases its oxygen content by 45 mL oxygen/L blood. This proposed value offers sufficient safety in acyanotic children but could be insufficient in cyanotic children that often have a low venous saturation requiring a higher oxygen transfer. For this reason, design of contemporary pediatric oxygenators allows oxygen transfers up to 75 mL/L at the nominal maximum flow given by the manufacturer. As a result, the reference flow (AAMI conditions) can be much higher (Table 3) than the recommended flow. Based upon this characteristic, one could use a smaller oxygenator, with the resulting lower hemodilution and contact activation, in selected cases (Durandy 2010a).

Table 3 Characteristics of pediatric oxygenators

Oxygenator	Membrane surface area (m^2)	Membrane material	Maximum blood flow (L/min)	Reference blood flow (L/min)	Heat exchanger surface area (m^2)	Connections (in.)	Priming volume (mL)	Maximum reservoir volume (mL)
Terumo FX05	0.5	PP	1.5	2.5	0.035			
Liva nova D100[a]	0.22	PP	0.7	1	0.03	3/16–1/4	31	500
Liva nova D101[a]	0.61	PP	2.5	3.5	0.06	1/4	87	1500
Maquet neonatal quadrox-i	0.38	PP	1.5	N/A	0.07	3/16–1/4	40	800
Maquet pediatric quadrox-i	0.8	PP	2.8	N/A	0.15	3/16–1/4	99	1700
Medtronic pixie[a]	0.67	PP	2	N/A	N/A	1/4	48	1200
Medos hilite 1000[a]	0.39	PP	1	N/A	0.074	1/4	57	700
Medos hilite 2800[a]	0.8	PP	2.8	N/A	0.16	3/16–1/4	98	1600

PP microporous polypropylene, *PET* polyethylene terephthalate, *N/A* not available
[a] No integrated filter

Priming and Hemodilution

Total priming volume of a CPB circuit depends upon the selected components (De Somer et al. 1996a). It is sometimes more beneficial to select a smaller oxygenator that will function close to its maximal capacity for flow than selecting a large oxygenator that will function toward its lower level. However, independent of the choice of oxygenator size its priming volume is predefined. Priming volume taken by the tubing, on the other hand, is determined by its length and diameter and mainly controlled by the surgical team (Ni et al. 2001). The total amount of priming volume is important, as it determines the dilution of the blood components. Composition of the priming fluid is an important point of consideration as it determines the final blood composition after mixing with the child's blood. Excessive dilution of blood coagulation factors below 45% should be prevented by using fresh frozen plasma in the priming solution (Brauer et al. 2013). This is especially important in cyanotic children as they have in general a lower plasma volume or in children with complex repairs (Pouard and Bojan 2013). As many institutions do not routinely screen coagulation factors before cardiac surgery, some centers use preoperative fibrinogen concentration as a surrogate reference. Ideally, postdilution fibrinogen concentration should be above 1 g/L.

A large variation between centers exists for target hemoglobin values during CPB. Literature reports values as low as 50 g/L up to 100 g/L (Nicolas et al. 1994; Gruber et al. 1999). Due to a lack of sufficient randomized prospective studies (Wilkinson et al. 2014), it is still unclear what is the optimal hemoglobin concentration during CPB. In practice, one should not focus solely on hemoglobin concentration, as the final oxygen delivery (DO_2) toward the organs depends on both hemoglobin concentration and pump flow. Consequently, one can tolerate lower hemoglobin concentrations as long as vascular access allows for high pump flows, but when anatomical or technical limitations limit the maximum blood flow, a higher hemoglobin concentration might be desirable. Following case gives an example of

the above for a child with a body surface area of 0.22 m^2. If target minimum DO_2 at normothermia for the child is 340 mL/min/m^2, required blood flow is 564 mL/min at a hemoglobin of 100 g/L, but this blood flow needs to double to 1130 mL/min in order to achieve the same target DO_2 at a hemoglobin of 50 g/L. It is obvious that the latter is less evident.

There is no proven benefit for the prophylactic use of a combination of fresh frozen plasma and packed red cells without solid clinical arguments (Wilkinson et al. 2014; Desborough et al. 2015).

Apart from the impact of the priming solution on blood coagulation and oxygen transport, its composition will also affect colloid oncotic pressure and electrolyte balance. There is evidence that maintaining a higher colloid oncotic pressure in neonates, by adding albumin, results in less fluid overload at the end of CPB in comparison to a pure crystalloid priming solution (Pouard and Bojan 2013).

Reflection on the composition of priming volume becomes even more important as more and more centers prefer normothermic conditions even for complex repairs such as transposition of the great arteries (Durandy 2010b).

In the early days of cardiac surgery, clinicians believed hemodilution was beneficial for the cardiac surgical population as it helped to reduce or avoid blood prime. Despite this advantage, it became obvious over the years, due to better monitoring techniques and extensive research, that hemodilution has its limits. Hemodilution will have a linear impact, when blood flow is constant, on total oxygen content. Diluting a patient with a hematocrit of 40% to a hematocrit of 20% decreases oxygen content per liter blood by 50%. In healthy patients, not on CPB, an increase in cardiac output compensates for this loss in oxygen-carrying capacity, facilitated by the reduced viscosity caused by the hemodilution. However, on CPB many centers use a fixed blood flow per square meter of body surface, typically between 2.2 and 3.0 L/min/m^2. Maintaining a fixed flow during excessive hemodilution may jeopardize oxygen delivery to the tissue, as the physiological compensatory increase in flow is absent.

Another disadvantage of hemodilution is the decrease in viscosity and plasma proteins. The decrease in viscosity leads to a loss in capillary density in the microcirculation (Tsai et al. 1998). Recent research showed that using fluids with a higher viscosity attenuates this negative effect. Increasing plasma viscosity correlates directly with increased perivascular nitric oxide concentration. Higher concentrations of local nitric oxide dilate and increase vascular density of the microcirculation in the organs (Tsai et al. 2005). Although the fluids used in this study had a viscosity higher than those commercially available, it seems favorable to use priming solutions with a higher viscosity (Manduz et al. 2008). A decrease in plasma proteins results in decreased plasma colloid oncotic pressure. Such a reduction may play an important role in the fluid accumulation observed after CPB. Tissue edema is secondary to increased capillary permeability caused by the systemic inflammatory response induced by CPB. In neonates, the combination of increased capillary permeability and the decrease of the colloid oncotic pressure seems to worsen the situation (Jonas 2004). Maintaining colloid oncotic pressure during bypass has been linked to decreased myocardial edema (Foglia et al. 1986) and reduced fluid accumulation. Lower fluid accumulation was associated with a shorter stay in intensive care and a lower mortality (Haneda et al. 1985).

Metabolism During CPB

The primary function of CPB is to maintain circulation in order to prevent organ dysfunction during and after surgical repair. Adequate oxygen delivery (DO_2) is one of the most important variables in achieving this goal. Oxygen delivery depends upon hemoglobin concentration and pump flow. In adults, it has been demonstrated that there exists a close correlation between the lowest hematocrit on bypass and morbidity (Habib et al. 2003). However, it is questioned whether this is due to the low hematocrit or due to a low DO_2 (Ranucci et al. 2005), which is the

combination of both hematocrit and blood flow. Recent research during normothermic (>32 °C) adult cardiac surgery showed that maintaining DO_2 above 280 mL/min/m^2 reduces the incidence of acute kidney injury from 29.8% to 12.1%. Transferring this value to the more heterogeneous pediatric population is not evident due to:

- Higher metabolism in neonates
- Presence of both cyanotic and noncyanotic children
- A broader range of hypothermia used during congenital heart surgery
- Different acid–base strategies (pH-stat versus α-stat)
- Existence of large intra- or extracardiac shunts

Despite those difficulties, recent research has established a cutoff value for DO_2 of 340 mL/min/m^2 at normothermia in neonates undergoing congenital cardiac surgery (Bojan et al. 2020; Reagor et al. 2020; Zhang et al. 2021). This value is reduced by 22 mL for each degree Celsius the patient is cooled. Maintaining DO_2 above this critical value attenuates the occurrence of hyperlactatemia and reduces the risk for AKI by 2.5 times. This underlines that when a center prefers a lower hematocrit during CPB, it must be compensated for by a higher blood flow. On the other hand, when anatomical limitations limit the size of the vascular access cannulas one should keep hematocrit higher during CPB.

The microcirculation is the ultimate destination of red blood cells to transport oxygen to the tissue cells. Its success defines the primary function of the cardiovascular system. Inside the microcirculation, there are two main determinants of oxygen transport to the tissue: convective transport of red blood cells to the capillaries and the passive diffusion of oxygen leaving the RBC to the mitochondria in the cells (Ince 2014). The formula for convective transport is:

$$DO_2 = \left[\left(\text{cte} \cdot \text{Hb} \cdot \text{S}\right) + \left(PO_2 \cdot k\right)\right] \cdot Q$$

where$Q$ is the blood flow [mL/min];
Hb is the hemoglobin concentration [g/mL];
cte = [1.34 mL/g];
S is the amount of oxygen bound to hemoglobin [%];
PO_2 is the partial oxygen tension [mmHg]; and
k is the oxygen solubility [mL/mL].

For a long time, the convective part of oxygen transport, being blood flow, was considered the sole factor to supply the microcirculation with oxygen. Today, one recognizes that the diffusion component of oxygen transport is at least as important as the convective component. The further away a tissue cell is from the oxygen-carrying red blood cell, for example, by excessive hemodilution (Atasever et al. 2011) or edema, the less time, even in the presence of sufficient flow within the capillaries, the oxygen has in reaching these cells. Diffusive capacity of the microcirculation depends upon the functional capillary density (FCD), which represents the number of capillaries in a given volume of tissue. Fick's law describes it as the product of the difference between the partial pressure of oxygen at the red blood cell minus that at the mitochondria, times the diffusion constant divided by the distance between the red blood cell and the mitochondria (Ince 2014; Boerma and Ince 2010). Immediately after and during CPB, there is a loss of FCD. The percentage loss depends upon the degree of hemodilution, viscosity, and the filling status of the microcirculation. In case of a decreased FCD, more cells become dependent from the oxygen supply delivered by a single capillary (Krogh 1919). Increasing cardiac output alone may be insufficient to correct the resulting tissue hypoxemia, and often there is need for microcirculatory recruitment procedures. Potential treatment options besides increasing flow are increasing partial CO_2 tension, increasing mean arterial pressure, and maintaining a normal viscosity. In order to validate the efficiency of the different options, NIRS is extremely helpful as it helps to define the pressure range in which the autologous regulation is maintained (Moerman et al. 2013).

A special group within the neonatal and pediatric CPB population is children with cyanotic heart disease. There is vivid debate on what is the best oxygenation strategy in this group, espe-

cially in the period before ischemia and during reperfusion of the myocardium after surgical repair. Maintaining high partial oxygen tensions in cyanotic patients at the beginning of CPB leads to reoxygenation injury with significant organ damage, including the myocardium, and triggers the systemic inflammatory response (Modi et al. 2002; del Nido et al. 1987, 1988; Caputo et al. 2014; Kagawa et al. 2014). One of the strategies proposed to avoid reoxygenation injury is the use of controlled reoxygenation. This technique targets an arterial partial oxygen tension (PaO_2) similar to the patient's preoperative oxygen saturation when starting CPB. Experimental models (Ihnken et al. 1995, 1998a) using this strategy showed less reoxygenation injury in adult patients (Ihnken et al. 1998b) and, more recently, in cyanotic pediatric patients with mixed pathologic features that are undergoing cardiac surgery (Caputo et al. 2009).

Another challenge is defining the best oxygenation strategy for children requiring deep hypothermia with circulatory arrest (DHCA) or hypothermia with low flow. Hypothermia slows down the metabolism. The relationship between cerebral metabolic rate for oxygen ($CMRO_2$) and temperature (McCullough et al. 1999) follows a log-linear model. However, even at a temperature of 20 °C, $CMRO_2$ is still 24% of baseline. Therefore, it is extremely important to ensure uniform cerebral hypothermia as it is critical for a successful outcome after DHCA. Cooling changes in oxygen binding to hemoglobin and in plasma solubility require special attention. Hypothermia shifts the oxygen dissociation curve (ODC) to the left. The P50 value, partial oxygen tension at which the hemoglobin is 50% saturated, is around 26.6 mmHg at 37 °C but will decrease to approximately 13 mmHg at 20 °C, making it more difficult to release hemoglobin-bound oxygen at tissue level. This has an important impact. At normothermia venous, oxygen saturation needs to decrease to 30% before $CMRO_2$ decreases to less than 90% of normal. However, in infants cooled to 17 °C venous oxygen saturation must be maintained at values greater than 95% to maintain $CMRO_2$ higher than 90% (Dexter and Hindman 1995). Due to this increase in hemoglobin's affinity for oxygen at 19 °C, 80% of the $CMRO_2$ will be no longer primarily provided by hemoglobin-bound oxygen but by dissolved oxygen (Dexter et al. 1997). In order to improve oxygen availability during DHCA, many centers use a pH-stat acid–base strategy. This approach targets a pH of 7.4 at the real blood temperature, e.g., 20 °C. The higher carbon dioxide content will shift the ODC more to the right, and P50 will increase from 13 mmHg to 15.3 mmHg. But pH-stat by itself is insufficient as the shift to the right is limited and needs companionship of measures to improve the amount of dissolved oxygen. Using hyperoxia is most effective. It is important to notice that the definition of hyperoxia in this context means a venous partial oxygen tension of >400 mmHg (Pearl et al. 2000). Increasing oxygen tension from 125 mmHg to 525 mmHg will increase the amount of soluble oxygen from 4 mL/L to 18 mL/L and increase safe DHCA time by 20 min in a child at 16 °C.

Because of the many variables involved, it remains a challenge to predict neurological outcome after DHCA or hypothermia with low flow. Children's Hospital Boston did an impressive amount of research in this domain looking at the impact of all variables discussed above. Based upon their research, the best approach for DHCA is the combination of hyperoxia with a higher hematocrit and pH-stat strategy. The hypothermia will decrease metabolic rate and, thus, increase the safe duration of DHCA, while the use of a higher hemoglobin and hyperoxia will allow for better hyperoxygenation of the brain before onset of DHCA. NIRS is a valuable tool for monitoring efficiency of hyperoxygenation and for monitoring remaining metabolism and oxygen consumption during DHCA. Depending on the degree of hyperoxygenation, the lower the metabolic rate, the longer it takes CMRO2 to reach a plateau with minimal oxygen extraction. The time between the onset of DHCA and the onset and duration of this plateau period are predictors of behavioral and histological evidence of injury after DHCA (Sakamoto et al. 2001).

Systemic Inflammation During CPB

Inflammation is the humoral and cellular protective response to injury (Davies and Hagen 1997). During cardiac surgery, a multifactorial systemic inflammatory reaction (SIRS) occurs. This reaction is triggered by almost every part of the procedure, starting with anesthesia (Gu et al. 2002), skin incision, and sternotomy, followed by the contact activation between blood and foreign surface of the CPB and later by the ischemia and reperfusion of the myocardium (Durandy 2014). Additional triggers are hypothermia and blood transfusions, which all affect the magnitude of the inflammatory response (Laffey et al. 2002). Activation of complement, coagulation, fibrinolysis, inflammatory cytokines, and cytodestructive mediators generated by white cells (Butler et al. 1993) are all part of SIRS. Initially, research to attenuate SIRS targeted systemic cytokines but it failed to link other host response systems to adverse clinical events (Landis 2009). Up to today, the clinical advances to attenuate SIRS have been disappointing.

Controlling Host Response

Despite systemic anticoagulation, Factor XII, fibrinogen, and globulins are absorbed onto the foreign surface of the CPB within seconds after initiation and generate thrombin in direct relation to CPB time (Brister et al. 1993; Boisclair et al. 1993). Activation of the coagulation cascade starts with tissue factor bearing white blood cells, such as monocytes. These will generate in response to injury small amounts of thrombin. This thrombin is sufficient to initiate hemostasis but not enough to cause thrombus formation (Monroe et al. 2002) as it can be rapidly scavenged by circulating antithrombin. However, in case of circulating activated platelets, thrombin will bind to them via the high-affinity thrombin receptor, protease-activated receptor-1 (PAR1), initiating several positive feedback loops. The latter is called the "amplification phase" and allows massive formation of thrombin generation that is essential for stable clot formation. When thrombin generation is not controlled during CPB, it may create both a prothrombotic risk to the grafted vessel as risk for systemic bleeding. The latter is due to the consumption of coagulation factors in combination with the unwanted activation of the platelet PAR1 receptor by thrombin (Landis 2009; Ferraris et al. 1998). The impact on platelet function by thrombin is an important cause of the clinical platelet deficit during and after CPB surgery and is witnessed by a drop in platelet count as a diminished capability to aggregate.

Proinflammatory activation of leukocytes and endothelial cells via bradykinin and PAR1 receptors expressed throughout the vasculature. (Kaplanski et al. 1997, 1998; Kamiya et al. 1993) is linked to kallikrein and thrombin and may explain some of the febrile and capillary leak symptoms seen after CPB (Landis 2009; Wachtfogel et al. 1995; Lidington et al. 2000). Inhibition of the proteolytic activation of PAR1 attenuates the proinflammatory activation of platelets and endothelial cells. (Day et al. 2006; Poullis et al. 2000). The beneficial effect of this approach was demonstrated in neonates with hypoplastic left heart syndrome, were the use of aprotinin improved survival after stage 1 repair (Tweddell et al. 2002).

Cardiopulmonary bypass activates the complement system via the classical pathway of C3, generated by IgM and IgG antibody adsorption by the CPB circuit (Landis et al. 2008). Several measures can help to control complement activation. Introduction of closed systems, smaller circuits, and coating of all foreign surface with a bioactive or biopassive coating all showed a small attenuation in complement and cytokine generation, but none of these measures could demonstrate major clinical improvements (De Somer et al. 2000; Eisses et al. 2007).

During the early phase of CPB, the direct contact between blood and foreign material leads to the generation of proinflammatory cytokines such as TNF-α, IL6 and IL8. This proinflammatory phase is followed by an anti-inflammatory phase, which occurs 2–24 h after initiation of CPB. It is characterized releasing anti-

inflammatory markers such as IL1 and IL10. The anti-inflammatory phase is mainly governed by the body (McBride et al. 1995).

The systemic host response depends also on leukocytes. Expression of the complement receptor CR3 on neutrophils and monocytes mediates leukocyte adhesion to polymers. Although phagocytosis of the polymers of the CPB circuit by these adhering cells is not possible, it will trigger the same cytodestructive inflammatory cytokine, protease, and reactive oxygen pathways that occur during genuine phagocytosis (Rothlein et al. 1994; Shappell et al. 1990). Another important source of oxidative stress is intravascular hemolysis, due to local areas of high shear stress in the CPB circuit (De Somer et al. 1996b). This shear stress will lead to the formation of free plasma hemoglobin. Another important source of free plasma hemoglobin generation is the aspiration of wound blood. The first defense mechanism against free plasma hemoglobin is haptoglobin, an inhibitor of free plasma hemoglobin. Once exhausted, free plasma hemoglobin can abrogate vasoprotective responses due to the scavenging of endothelial nitric oxide and may accumulate in the proximal tubules, causing direct renal injury, especially in patients with diabetes (Minneci et al. 2005). Peak oxidative stress due to hemolysis is mostly observed after the release of the cross-clamp as this is the moment when most wound blood is aspirated from the mediastinal and pleural cavities and precedes inflammatory cytokine generation (Christen et al. 2005). A significant contribution to the "systemic inflammatory response" may therefore be due to oxidative stress and loss of vascular nitric oxide responses secondary to hemolysis. Avoiding or controlling aspiration of blood from the surgical field will attenuate free plasma hemoglobin generation and activate blood platelets. Separating this blood from the systemic blood has shown to improve outcome (Aldea et al. 2002).

From the above, it is clear that we should replace the terminology systemic inflammatory response by a definition that is emphasizing the multisystemic etiology of this disorder such as systemic "host" response to surgery. Interventions should focus to target multiple effector pathways simultaneously. In order to increase knowledge, studies should better report the observed systemic host response. A consensus paper looking at the published research pointed out that better reporting should comprise (1) minimal CPB and perfusion criteria that may affect outcomes, (2) causal inflammatory markers that link exposures to outcomes, and (3) markers of organ injury that are practical to measure yet clinically meaningful (Landis et al. 2008).

Conclusions

Instituting CPB in a neonate or child for correction of congenital heart disease remains a challenge. Future research should focus on:

- Further miniaturization of the CPB circuit
- Improved vascular access
- Better strategies to control inflammation
- Better understanding of fluid homeostasis during and after CPB.

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Atrioventricular Septal Defect (AVSD)

Ali Dabbagh and Iki Adachi

Abstract

Atrioventricular septal defect (AVSD) is a collective term for myocardial tissue deficiency at the atrioventricular (AV) junction. Other names have been used: AV canal defect, common AV orifice, endocardial cushion defect, etc. AVSD occurs in 2 out of 10,000 live births, approximately at the fifth week of gestation, i.e., when the "*endothelial to mesenchymal transition of endothelial cells*" happens.

The main pathologies include the common AV junction, the septal defects, the left ventricular outflow tract, and the five-leaflet common AV valve.

The clinical presentations include heart failure, failure to thrive, and presentations of pulmonary hypertension or pulmonary overflows; however, cyanosis is usually either mild or absent.

Surgical approaches include the "traditional single-patch technique," "standard two-patch technique," "modified single-patch technique, i.e., Australian technique," and "no-patch technique." During the surgery, the degree of shunting, management of pulmonary hypertension, ventricular failure (right and/or left ventricle), low cardiac output state, AV valve regurgitation, AV conduction block, and defects in surgical repair and/or residual shunt should be considered cautiously. Also, airway management could be a real challenge, especially in trisomy 21 patients.

The overall mortality rate for AVSD repair is low, though some risk factors may lead to poor outcomes.

Keywords

Atrioventricular septal defect · Endocardial cushion · Congenital heart disease
Atrioventricular canal defect · Common atrioventricular valve · Trisomy 21

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Introduction

Atrioventricular septal defect (AVSD) is a collective term for a spectrum of congenital heart disorders that are characterized by a deficiency of

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myocardial tissue at the atrioventricular (AV) junction. This group of hearts is also described as:

- Atrioventricular canal defect
- Common atrioventricular orifice
- Endocardial cushion defect
- Ostium primum atrial septal defect

AVSD occurs in 2 out of every 10,000 live births (Calabro and Limongelli 2006).

Cardiac Anatomy and Embryology

Since congenital heart diseases result from abnormal development of the heart during fetal life, understanding cardiac embryology helps to explain how various cardiac malformations have developed. Nonetheless, it must be noted that many of the embryologic explanations remain speculative without concrete evidence. It may be safer, therefore, to use the knowledge in embryology as a tool for a better understanding of cardiac anatomy rather than to consider it as a scientific fact. The main etiologic mechanism of AVSD is believed to be impaired development of the "endocardial cushions"; hence, the term "endocardial cushion defect" is applied. Some researchers consider the endocardial cushions as the "forerunners" of the AV valves (Gaussin et al. 2005; Nayak et al. 2020; Ahmed and Anjum 2021; Rigby 2021; Taqatqa and Vettukattil 2021).

AVSD occurs approximately at the fifth week of gestation, i.e., when the superior and inferior endocardial cushions are going to be created and appeared over the primitive left ventricle (Ray and Niswander 2012). The cells that constitute the endocardial cushion tissues are primarily endocardial in origin; however, these endothelial cells migrate into the inner layers of the heart tube to create the primitive mesodermal tissue of this tube, which is located in the crux of the heart. This critical process in the formation of cardiac cushions is called "*endothelial to mesenchymal transition of endothelial cells*" in cardiac cushions (Zhang et al. 2014; Davey and Rychik 2016; Taqatqa and Vettukattil 2021).

A range of cellular and molecular factors play a role in the development of cardiac cushions; as demonstrated in the previous animal models, any impairment in each of the latter may lead to endocardial cushion defects (Yamagishi et al. 2009; Moskowitz et al. 2011; Ray and Niswander 2012; Garside et al. 2013; Liu et al. 2013; Kathiriya et al. 2015; Stefanovic and Christoffels 2015; Bhakta et al. 2019; Hong et al. 2021):

- Transforming growth factors and proteins (like bone morphogenetic protein [BMP]) and their controller molecules
- Intercellular signaling molecules and enzymes
- Transcription factors and mutations in their related genes, like GATA4 transcription factor, TGF beta, FOG factor, Smad4, Zic family member 3 (Zic3), NK2 homeobox 5 (Nkx2.5), SOX family of transcription factors, and T-box protein 5 (Tbx5)
- Extracellular matrices

The role of genetic diversity and genetic detection in AVSD patients has become more prominent during the last few years (Xu et al. 2018).

The abnormal development of the endocardial cushions results in the defect in the septum at the crux of the heart and the loss of normal development of the AV valves. Since the degree of abnormalities in the septum and the AV valves varies considerably, there are different phenotypes within the spectrum of AVSD. The cardiac morphology and physiology of AVSD are more understandable if one takes the following pathologic features into account:

1. *The common atrioventricular junction*: In normally structured hearts, the AV junction is "Figure 8-shaped," with two separate junctions for the mitral and tricuspid valves. In hearts with AVSD, there is no separation of the two junctions, forming a common "oval-shaped" ring, also known as the "common atrioventricular valvar junction" (with often but not always with five leaflets).

2. *The defect in the septal structure*: In virtually all hearts with AVSD, there is a defect in the septum at the crux of the heart. Depending on the relationship between the AV valves and the septal defect, the defect can be at the ventricular level, at the atrial level, or at a combination of both. For example, when the AV valve leaflets are completely adherent to the undersurface of the atrial septum, the resultant defect will limit the intracardiac shunting at the ventricular level (i.e., so-called AV canal-type VSD). On the other hand, if the AV leaflets are completely adherent to the crest of the ventricular septum, the shunting will be only at the atrial level (i.e., ostium primum defect). In other forms, the leaflets of the common AV valve close neither, leaving the shunting at both the atrial and ventricular levels (i.e., complete AVSD) (Wenink and Zevallos 1988; Adachi et al. 2008, 2009a, b, c).
3. *Left ventricular outflow tract*: The pathologic feature of the AV valve junction (loss of the normal figure 8-shaped ring and resultant *oval-shaped ring*) impacts the morphology of the left ventricular outflow tract (LVOT). In normally structured hearts, the aorta is cradled in the waist of the figure 8-shaped AV junction. By contrast, the aorta is located more anteriorly in AVSD because of the loss of the "waist" at the AV junction due to the oval-shaped ring. Such an anterior location of the aorta will make the LVOT elongated, called "*anterior scooping*" of the aorta. In normal hearts, the LVOT length (i.e., the length from the cardiac apex to the aortic valve) is approximately equal to the LV inflow length (i.e., the length from the cardiac apex to the mitral valve). In AVSD, however, the LVOT length is increased relative to the inlet length. This anatomical feature is responsible for the typical angiographic appearance and is known as "*gooseneck deformity*": Figs. 1, 2 and 3 (Craig 2006; Mahle et al. 2006; Adachi et al. 2008, 2009a, b, c; Shuhaiber et al. 2009; Chauhan 2018; Ahmed and Anjum 2021; Maurer et al. 2021; Rigby 2021).

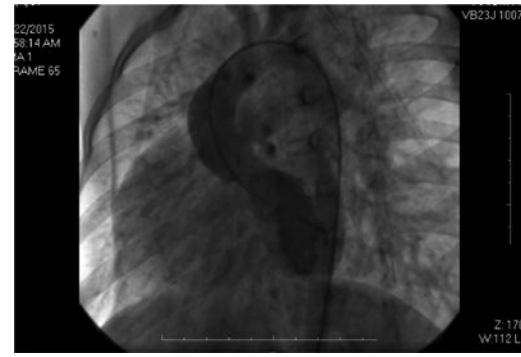

Fig. 1 Angiographic presentation of AVSD known as "Gooseneck deformity" before the start of systole

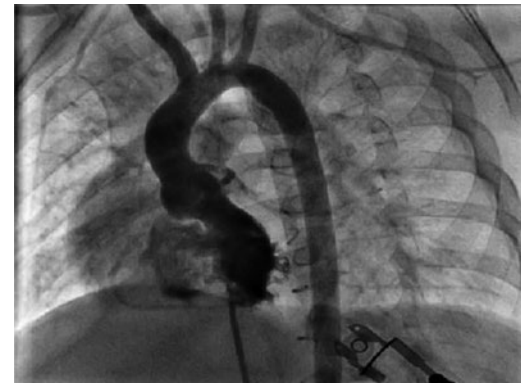

Fig. 2 Angiographic presentation of AVSD known as "Gooseneck deformity" in systole

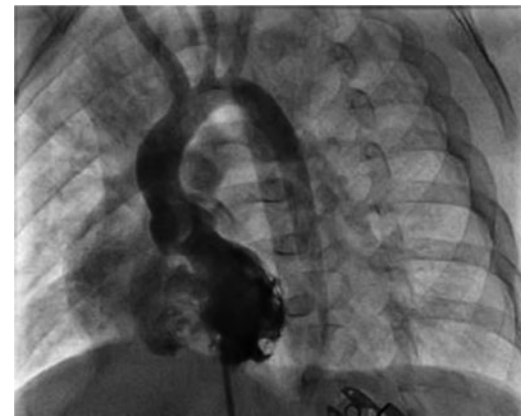

Fig. 3 Angiographic presentation of AVSD known as "Gooseneck deformity"in early systole

Pathologic Findings and Associated Anomalies

The three main mechanisms described in the previous section lead to the pathologic findings seen in AVSD; all of them are the result of the main faulty developmental defect, i.e., *endocardial cushion defect*. The main pathologies found in patients with AVSD are the following (Craig 2006; Adachi et al. 2008, 2009c; Chauhan 2018; Ahmed and Anjum 2021; Maurer et al. 2021; Rigby 2021):

1. In normal hearts, each AV valve has a separate annular ring: one for the mitral valve and the other for the tricuspid valve. In hearts with AVSD, there exists *only one common valve ring*, i.e., just we could imagine that the AV junction failed to separate during fetal life, resulting in one common AV valve ring. This common annulus does not follow the normal figure 8 configuration seen in normal AV valves; instead, one oval ring exits for connecting between atria and ventricles.
2. Normal mitral and tricuspid leaflets are not seen anymore; instead, a special anatomic configuration exists in these leaflets often described under the *Rastelli classification*. The common AV valve typically, but not always, has a five-leaflet configuration with a common AV valve annulus (i.e., complete AVSD). Occasionally, there are two AV valve annuli within the common AV valve junction if a piece of tissue "band" divides the common AV valve into two separate orifices (i.e., partial AVSD). The two orifices create separate right and left passages for blood. Despite having two AV valve annuli, however, these hearts still have a common AV valve junction, which is the fundamental feature of AVSD.
3. The pathologic annulus (i.e., oval-shaped common AV valve junction) decreases the space needed for the LVOT and aorta to emerge from the left ventricle; so, there is an anterior deviation and tendency for the aorta and LVOT named "*anterior scooping*" of the aorta; Figs. 1, 2 and 3 (Adachi et al. 2009a, b).
4. The anterior scooping of the aorta lengthens the course of blood movement from the LV through LVOT; in normal hearts, the distance from the mitral valve to the LV apex (i.e., the LV inlet) is approximately equivalent to the distance from the LV apex to the aortic valve (i.e., LV outlet), causing the LV outlet/inlet ratio of 1/1. In AVSD, however, this ratio is increased due to anterior scooping of LVOT.
5. Orientation of the papillary muscles is different in hearts with AVSD. For example, the papillary muscles of the left AV valve in AVSD have more or less *superior–inferior orientation*, while the papillary muscles of the normal mitral valve have oblique orientation.
6. Defects in the interatrial septum with resultant shunting at the atrial level ("*ASD primum*") are seen often in hearts with AVSD. There exist hearts with AVSD but not having primum ASD. This rare subset is called "AVSD with only ventricular component" (Adachi et al. 2009c). This rare form of AVSD is not often seen in the clinical setting in part because this anatomy is considered as "AV canal type VSD" or "inlet VSD." However, it must be remembered that what differentiates hearts with AVSD from VSD is the presence of a common AV valve junction. Regardless of the level of intracardiac shunting, the hearts should be categorized under the spectrum of AVSD if there is a common AV junction.
7. Defects in the caudal and posterior section of the ventricular septum create shunting at the ventricular level (as seen in *intermediate* and *complete* types of AVSD). As mentioned above, the ventricular level defect is often called "*inlet type VSD*." However, care must be taken to use this terminology since "VSD" implies there is a normal separation of the AV valve junctions.
8. The common AV valve typically has a five-leaflet configuration:
   (a) Superior bridging leaflets (SBL) (also named anterior bridging leaflet)

(b) Inferior bridging leaflets (IBL) (also named posterior bridging leaflet); both SBL and IBL cross over the interventricular septum; also, each of these two leaflets are attached to both right ventricle and left ventricle through chordae tendineae, though the chordae and their anatomic arrangement are different from normal
(c) Right anterolateral leaflet
(d) Right mural leaflet
(e) Left mural leaflet

Classification of AVSD

In general, hearts with AVSD are classified into three subtypes based on the level of intracardiac shunting (Jacobs et al. 2000; Craig 2006; Adachi et al. 2008, 2009c; Shuhaiber et al. 2009; Buratto et al. 2014; Xie et al. 2014; Ahmed and Anjum 2021; Maurer et al. 2021):

- *Complete AVSD* (both atrial and ventricular level shunting with a common AV valve). Complete AVSD is further subdivided into "Rastelli type A," "Rastelli type B," and "Rastelli type C" depending on the status of the superior bridging leaflet relative to the crest of the ventricular septum; a detailed description of Rastelli classification could be found in selected references.
- *Partial AVSD* (so-called "*ostium primum ASD*" plus "*cleft mitral valve*") in which a tongue of tissue attaches the two "SB and IB" leaflets to create two separate orifices in the common AV valve; however, these two orifices are never true valves because they do not have the real structure of separate and complete annulus, and their leaflets have a minimal resemblance to the leaflets of the normal hearts.
- *AVSD with only ventricular component* (typically described as "*AV canal-type VSD*"). This subtype of AVSD represents the mildest form of hearts with AVSD within the spectrum of AVSD. It is the least common form of the disease.

Associated Cardiac Anomalies

At times, AVSD is accompanied by some other cardiac malformations that complicate perioperative management and surgical procedure. The following cardiac anomalies may accompany AVSD (Craig 2006; Tchervenkov et al. 2006; Mitchell et al. 2007; Shuhaiber et al. 2009; Karl et al. 2010; Maurer et al. 2021):

- Tetralogy of Fallot (which is associated with complete AVSD and its combination results in RVOTO in AVSD)
- Left ventricular outflow tract obstruction (congenital LVOTO)
- Subaortic stenosis
- Double outlet right ventricle (DORV)
- Truncus arteriosus (or common arterial trunk)
- Common AV valve with single ventricle pathology
- Left AV valve with double orifice
- Unbalanced complete AVCD
- Transposition of great arteries (TGA)
- Atrial isomerism (left or right type of isomerism)

Clinical Presentation and Diagnosis of the Disease

The clinical findings in AVSD usually present with signs and symptoms of heart failure and failure to thrive, both of them with varying degrees. Also, cyanosis is usually either mild or absent. The findings related to pulmonary hypertension or pulmonary overflows like tachypnea and reduced activity may be seen.

ECG findings are the result of anatomic abnormalities in the interventricular septum (Fig. 4):

- P wave abnormalities including superior P wave axis are seen in patients with left atrial isomerism; superior axis deviation is considered as one of the most characteristic findings in AVSD patients.
- AV node displacement from its normal position is seen, leading to an enlarged bundle that

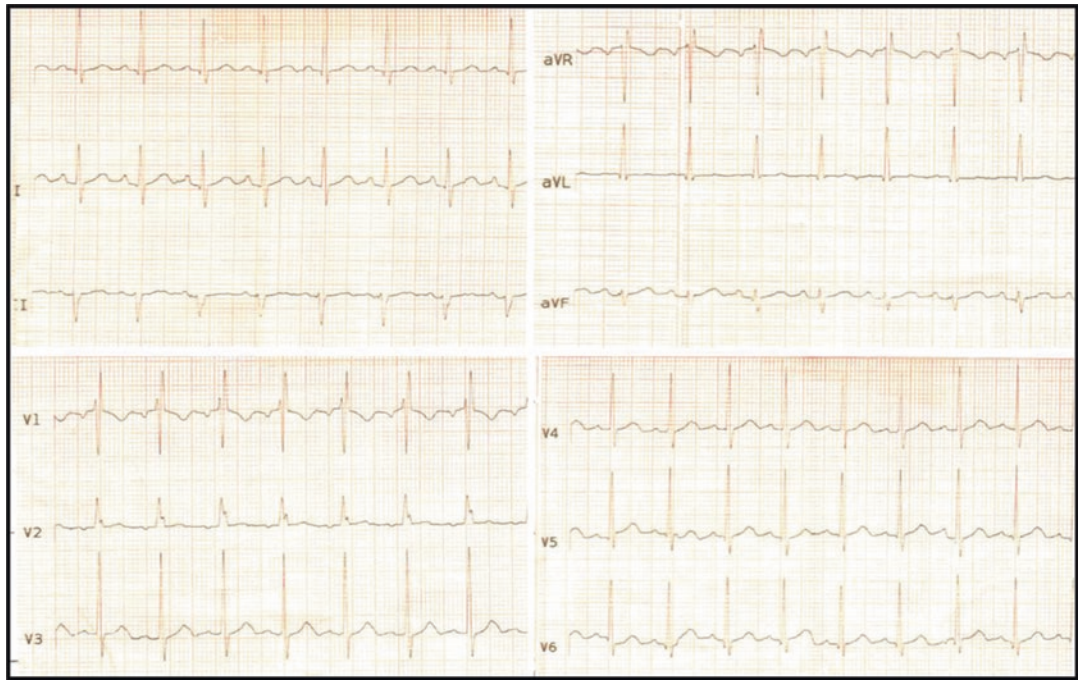

Fig. 4 Complete AVSD with left axis deviation, incomplete RBBB, and biventricular hypertrophy. (Courtesy of Dr. Majid Haghjoo and Dr. Mohammadrafie Khorgami)

paves its course alongside the ventricular septum.

- Axis has deviated from −40 to −150.
- Prolongation of the PR interval due to intra-atrial conduction delay may be seen in about 50% of patients (first degree AV block).
- Right bundle branch block (RBBB) is seen (usually partial block).
- RVH pattern is always seen; however, LVH may be observed.
- *The most characteristic finding* in AVSD is the superior orientation of the frontal QRS wave, i.e., superiorly oriented counterclockwise QRS loop; this loop resembles "a figure-of-eight QRS loop," which lies on the upper part of the isoelectric line in the frontal plane; QRS is usually rSr´ or rsR´; also, QRS has moderate-to-severe left axis deviation (Feldt et al. 1970; Craig 2006; Khairy and Marelli 2007; Adachi et al. 2009c; Ahmed and Anjum 2021).

Echocardiography

Nowadays, fetal cardiac diagnosis using antenatal echocardiography is commonly used in AVSD patients with impressive results (Taqatqa and Vettukattil 2021).

During the intraoperative period, transthoracic echocardiography is the method of choice for preoperative diagnostic assessment. Intraoperative transesophageal echocardiography (TEE) provides even more detailed information necessary for surgical repair. These findings can be seen in intraoperative TEE (Craig 2006; Cohen and Stevenson 2007):

- Right ventricular (RV) hypertrophy
- Right atrial (RA) hypertrophy
- ASD
- VSD: its severity depends on the subtype of the disease

- Different degrees of tricuspid regurgitation (TR), which would depend on the structure of the right side of the AV valve, and also, the severity of pulmonary hypertension
- Pulmonary artery dilation, especially when an overflow of the pulmonary system is a marked finding
- Subvalvular aortic stenosis (due to the effects of mitral chordae and scooped aorta), though not a common finding, could be seen in some patients and mandates sophisticated TEE assessments following surgical correction immediately after weaning from bypass

Surgical Repair

Some factors impact the outcome of surgical repair for AVSD, which include the repair technique, underlying chromosomal abnormalities, severity of the disease and its subtypes seen in each patient, other associated cardiac anomalies, the severity of regurgitation in common AV valve, age-matched *z* scores, and several other factors (Craig 2006; Halit et al. 2008; Karl et al. 2010; Ong et al. 2012; Taqatqa and Vettukattil 2021).

The first successful repair of AVSD was performed in 1954 on a 17-month-old girl by Lillehei et al. Since then, different approaches have been used for the repair of AVSD (Wilcox et al. 1997; Nicholson et al. 1999; Backer et al. 2007; Nunn 2007; Halit et al. 2008; Shuhaiber et al. 2009; Jonas and Mora 2010; Vida et al. 2016):

1. "*Traditional single-patch technique*" utilizes one patch for closure of both ASD and VSD. The AV valves are divided into the right and left components and sutured to the single patch through a right atriotomy.
2. "*Standard two-patch technique*" uses two separate patches for ASD and VSD, usually, pericardium for ASD and one "pericardium, PTFE, or Dacron patch" for VSD.
3. "*Modified single-patch technique*" or "*Australian technique*" described by Nicholson and Nunn in 1999 uses primary suture for VSD closure, i.e., as they described, they used "direct suturing of the common AV valve leaflets to the crest of the ventricular septum without using any material." The fundamental feature of this technique is a conversion of complete AVSD anatomy into "ostium primum ASD" anatomy, by suturing down the AV valve tissue directly on the crest of the ventricular septum. Owing to its simplicity, this technique has been gaining more popularity over the last decade. Some believe that this technique is best appropriate for younger patients (with an ideal age of 4 months). This technique results in significantly shorter bypass time and cross-clamp time (Nicholson et al. 1999; Geoffrion et al. 2018). Care must be taken, however, that this technique can result in distortion of the AV valve if the VSD component is very deep or asymmetrical (Adachi et al. 2009b). Though the technique needs shorter cardiopulmonary bypass and cross-clamp time, the postoperative outcome either remains unaffected or is not significantly improved (Li et al. 2017; Fong et al. 2019; Loomba et al. 2019).
4. "*No-patch technique*" uses the common AV valve tissue for closing ASD and VSD.

Often, in these methods of repair, a right atriotomy is used, several maneuvers are done for the preservation of the His bundle, the AV valve is repaired to prevent excessive postoperative regurgitation (sometimes annuloplasty is added to further correct the valves), and a left atrial catheter is placed and fixed as the final step before weaning from bypass by the surgeon.

Intraoperative Management of Anesthesia

Table 1 demonstrates, in brief, the main challenges in the anesthetic management of AVSD patients (Craig 2006; Shuhaiber et al. 2009). There are several modalities used for the management of pulmonary hypertension before, during, and after CPB including (Craig 2006; Shuhaiber et al. 2009):

Table 1 Main challenges in the anesthetic management of AVSD

Degree of left to right shunting
Management of pulmonary hypertension and RV failure
LV dysfunction and low cardiac output state (LCOS)
AV valve regurgitation (mitral regurgitation and/or tricuspid insufficiency)
AV conduction block and/or arrhythmias
Defects in surgical repair and/or residual shunt
Airway management could be a real challenge, especially when considering the large size of the tongue in trisomy 21 patients

- Sophisticated multimodal cardiac monitoring includes invasive blood pressure, TEE, NIRS, left atrial pressure, cardiac output monitoring, and other modes of monitoring, which should be tailored for each patient.
- A combination of inotropes and vasopressors to augment hemodynamics adjusted by the use of monitoring data.
- Use of inhaled nitric oxide (NO).
- Management of ventilation parameters to prevent overt PEEP and/or hyperventilation.
- Controlling depth of anesthesia using enough analgesics.
- Prevention of hypothermia.

On the other hand, elevated filling pressures should be avoided in ventricles to prevent annular dilation of the AV valves and hence, prevent AV regurgitation; a left atrial pressure catheter is a useful monitor; LA pressure in the range of less than 10 mmHg is considered appropriate for weaning from cardiopulmonary bypass.

Postoperative Care for AVSD

In some patients, particularly those with chronic lung disease, it may take time to discontinue ventilator support. Again, invasive blood pressure monitoring, NIRS, adequate pain management, management of blood pressure using inotropes and/or vasopressors, prevention of pulmonary hypertension using adequate analgesics, and pulmonary vasodilator strategies are among the main therapeutic methods used for postoperative care of these patients.

Reoperation

Early reoperation: Early reoperation is necessary when there is a residual gap or any other suboptimal results of surgery, including severe AV valve regurgitation, LVOTO, or RVOT; the latter is usually seen when AVSD and TOF are superimposed (Shuhaiber et al. 2009; Bianchi et al. 2011; Raisky et al. 2014). Careful assessment with TEE after weaning from cardiopulmonary bypass should eliminate the need for early reoperation.

Reoperation in adults: Based on the ACC/AHA 2008 Guidelines, the following are the main indications for reoperation in adults (Warnes et al. 2008):

- Left AV valve regurgitation and stenosis, which are symptomatic, cause arrhythmias (atrial or ventricular) or lead to the progressive increase in dimensions of LV, or deterioration of LV function; these need either valve repair or valve replacement.
- LVOT obstruction, which has a mean gradient of more than 50 mmHg or a peak instantaneous gradient of more than 70 mmHg, or LVOTO with a gradient less than 50 mmHg but associated with significant mitral regurgitation or aortic regurgitation.
- Residual and/or recurrent ASD or VSD with significant left-to-right shunt.

Outcome

The overall mortality rate for AVSD repair in experienced centers is in the range of 1–3%. This is, however, largely dependent on the presence or absence of other factors such as prematurity, chronic lung disease, and chromosomal abnormalities. Mortality doubles with associated lesions especially if there are ≥2 major noncardiac anomalies. The best outcome is obtained if repair is performed before the patient develops a significant pulmonary disease. Approximately, the age of 3–6 months would be considered appropriate for surgical repair, although it must be emphasized that pulmonary vascular disease can progress much quicker in some patients. The

outcome of the patients does not seem to be overly influenced by the presence of trisomy 21; though, some believe AVSD patients with trisomy 21 may have a better outcome. Anecdotally, patients without trisomy 21 tend to have more complex and dysmorphic AV valve morphology. The occurrence of left AV valve incompetency as well as LVOT obstruction is a potential complication in the intermediate to long term. Also, the surgical technique could affect the outcome; however, we have to wait to see which surgical technique would provide a definite superior outcome in the long term (i.e., single-patch, modified single-patch, or two-patch techniques); however, some items have unwanted effects on the outcome including "an atrial communication at biventricular repair of AVSD" (Tchervenkov et al. 2006; Shuhaiber et al. 2009; Miller et al. 2010; Atz et al. 2011; Bianchi et al. 2011; Raisky et al. 2014; Xie et al. 2014; Calkoen et al. 2016; Callahan et al. 2021).

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Atrial Septal Defect, Ventricular Septal Defect

Ali Dabbagh

Abstract

Atrial septal defect (ASD) is the general name for multiple cardiac lesions whose etiology is mainly a congenital defect in the interatrial septum. Atrial septal defects, after bicuspid aortic valve and mitral valve prolapse, are the third most common congenital heart disease. Atrial septal defects are much more frequent in women than men. A long list of assessment methods is used to detect the disease, from noninvasive ones to fully invasive methods. The management depends on both the underlying type of lesion and the general condition of each patient. The outcome is often fair.

Ventricular septal defects (VSDs) are also among the most common congenital heart diseases, being the most common congenital defect at birth up to 40% of all congenital heart diseases. VSDs may involve the interventricular septum (IVS) as an isolated defect, as part of the other congenital disease(s), or as a part of complex congenital heart disease including (but not limited to) the following diseases:

- Conotruncal defects,
- Tetralogy of Fallot,
- Transposition of great arteries,
- Congenitally corrected transposition,
- Double outlet right ventricle,
- Double outlet left ventricle,
- Left-sided obstructive lesions,
- Subaortic stenosis,
- Aortic coarctation,
- Interrupted aortic arc.

Also, there is an important classification of the lesion based on anatomic and embryologic origins. Different diagnostic methods are used to detect the disease. Most small VSDs close spontaneously during the first year of life, while the larger ones or "multiple VSD" cases usually need intervention. If untreated, pulmonary hypertension and systemic desaturation may ensue. Although spontaneous closure is a common phenomenon in infancy and childhood, it occurs much less frequently in adulthood.

Keywords

Congenital heart disease · Atrial septal defect Ventricular septal defect · Pulmonary hypertension · Anesthesia · Surgery

Atrial Septal Defect

Introduction

Atrial septal defect (ASD) is the general name for multiple cardiac lesions whose etiology is mainly

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a congenital defect in the interatrial septum. Atrial septal defects, after bicuspid aortic valve and mitral valve prolapse, are the third most common congenital heart disease. Atrial septal defects are much more frequent in women than men (McCarthy et al. 2003; Geva et al. 2014; Menillo et al. 2021).

Embryology

Detailed discussions on the embryology of ASDs can be found in chapter "Cardiovascular System Embryology and Development"—Cardiovascular System Embryology and Its Development; however, a brief discussion is presented here. The septation process is an embryologic stage leading to chamber formation. Interestingly, only the "eutherian mammals" undergo a "two-septal development process" for the creation of the atrial septum, a process that is error-prone, leading to "incomplete closure of the atrial septum" which is known as "probe patency" (Jensen et al. 2019). This process in the common atrium starts at the beginning of the fifth week and includes the following steps (Anderson et al. 2003; McCarthy et al. 2003; Gittenberger-de Groot et al. 2005; Sukernik and Bennett-Guerrero 2007; Geva et al. 2014; Asrress et al. 2015; Calkoen et al. 2016; Kloesel et al. 2016; Jensen et al. 2019):

1. A sickle-formed crest comes down from the roof of the common atrium which makes *septum primum.*
2. The *septum primum* develops caudally towards the endocardial cushion in the atrioventricular canal.
3. Now, *ostium primum* is in the common atrium, allowing interatrial blood flow.
4. Superior parts of the septum primum are fenestrated by apoptosis thereby creating *ostium secundum* allowing the right to left shunt in the fetal circulation; the obliterated superior part of the septum primum will be completed by *septum secundum.*
5. From the common atrial wall roof, a crescent muscular mass grows downward on the right side of the septum primum producing the superior parts of the interatrial septum; it covers the main part of the *ostium secundum* and is called the *septum secundum.*
6. Now, we nearly have the future interatrial septum which is composed of two merging septa: *septum primum* and *septum secundum,*
7. There is a defect in the septum secundum called *fossa ovalis* which is usually compensated by *septum primum*. However, a wide range of defects may affect fossa ovalis and hence, create gaps or deficiencies in the flap valve.
8. Also, there is *foramen ovale*, a defect in the borders of septum primum and septum secundum, which is an obliquely elongated cleft in the interatrial septum—it will be open as long as fetal circulation persists. After birth, due to the transition from fetal circulation to normal circulation, pressure in the left cardiac chambers increases, and foramen ovale is closed; the closure is a physiologic one in the first steps; however, it will be changed to an anatomic closure after a while, anatomically,
9. Pulmonary veins are relocated from the right atrium to the left atrium.
10. *Sinus venosus* is the part of tissue separating right pulmonary veins from the superior vena cava (SVC) posteriorly and also, the inferior aspects of the free right atrium wall. The *coronary sinus septum* is the part of myocardial tissue separating the coronary sinus from the left atrium. Also, the left venous valves and the septum spurium merge with the right side of the septum secundum.

Classification

In this section, the classification of the most common types of ASDs based on the above embryological sequence of events is presented in Table 1. (Kerut et al. 2001; Sukernik et al. 2001; Oliver et al. 2002; McCarthy et al. 2003; Van Praagh et al. 2003; Ashley 2004; Sukernik and Bennett-Guerrero 2007; John et al. 2011; Briggs et al. 2012; Asrress et al. 2015).

Table 1 Classification of atrial septal defect (ASD) lesions

Type of ASD	Mechanism of ASD	Occurrence of the lesion/clinical outcome	Associated lesions
ASD secundum (ASD II)	Failure in pulling-down of septum primum and deficient septum secundum	The most common type of ASD; 70% of all ASDs are ASD II; 65–70% of ASD II are female; about half of them are closed spontaneously; the chance of spontaneous closure is more in smaller size defects and less than 1 year age; increasing age and larger defects less chance for spontaneous closure	Mitral valve prolapse Mitral valve stenosis Pulmonary stenosis
ASD primum (ASD I)	If the ostium primum is not closed by the septum primum an ASD I result; ASD I is located close to the atrioventricular valves and is often associated with an atrioventricular septal defect	50% of ASD I patients are female; usually, surgical treatment is often mandatory for closure of ASD I because there is very little chance for spontaneous closure	Cleft mitral valve (always) Inlet ventricular septal defect Septal aneurysms
Sinus venosus type ASD (SVASD)	SVASD is an unusual type of ASD, with two common locations: If located superiorly, it is near the entry of SVC If located inferiorly, it is near the entry of IVC It is often associated with anomalous attachment of venae cavae and pulmonary veins Often, due to these anatomic locations, it is discussed under partial anomalous pulmonary venous drainage	40–50% of SVASD patients are females There is usually no spontaneous closure—surgical treatment is often mandatory	Partial anomalous venous return Overriding superior vena cava
Coronary sinus septal defect (CSSD)	CSSD occurs if the delicate tissue separating the coronary sinus from the left atrium is not completed; the result is blood shunting through the defect and the orifice of the coronary sinus	An uncommon type of ASD	Unroofed coronary sinus Left superior vena cava persistence Partial/total anomalous venous return
Persistent foramen ovale (PFO)	The pathologic defect is the same as the pathology if fetal circulation persists (Persistence of Fetal Circulation: PFC) which is associated with increased pressure on the right side	PFO, as an independent lesion, is present in as much as 25% of the general population Its occurrence should be considered independently from defects in the interatrial septum	Similar to PFO

Pathophysiology of ASD

Due to ASD, during the early course of the disease, oxygenated blood flows from left to right, leading to the following events (Oliver et al. 2002; Azarbal et al. 2005; Tobis and Azarbal 2005; Warnes et al. 2008; Geva et al. 2014; Zvaigzne et al. 2014; Jensen et al. 2019):

- In nearly all ASD patients, there are varying degrees of the interatrial shunt; if the pressure is higher on one side, the blood would shunt from that side to the other side.
- Often, there is a *left-to-right shunt* in ASD patients; the severity of the shunt and its direction depends on two main factors: the *size of the defect* in the inter-atrial septum and *left*

and right atrial pressures and the relationship between them.
- In ASD secundum, if the defect is less than *10 mm*, the amount of shunt is usually negligible and the severity of right heart overload and pulmonary hypertension is very low.
- If the defect is large enough to induce considerable shunt flow, then, the lungs are overflowed due to the *recirculation of oxygenated blood* to the lungs.
- Increased blood volume load to the lungs often leads to *enlargement of the right heart chambers* (right atrium and ventricle) often associated with impaired function of the right atrium. Also, the pulmonary and right heart vascular systems (both arteries and veins) are enlarged due to pulmonary overflow.
- Over time, pulmonary overflow, pulmonary vascular bed remodeling, ventricular remodeling, and trophic changes in the right and left ventricles lead to *pulmonary hypertension* with different severities. The incidence of right heart failure and pulmonary vascular disease is more prevalent in female patients compared with male patients and also in untreated adults.
- Additionally, decreased blood flow through the left heart leads to shrinkage or compromised growth of the left ventricle and aorta—the final result could be diminished systemic output and finally, *left ventricular systolic dysfunction.*
- If pulmonary hypertension persists and the process of shrinkage in the aorta and left ventricle continues, *Eisenmenger syndrome* may develop. This presents as increased pulmonary pressure over the systemic pressure accompanied by different degrees of right heart failure.
- Often, in the course of the disease, *exercise intolerance* occurs due to impaired hemodynamics, although it is not a common event during the early stages of the disease; however, with advanced age, intolerance increases insidiously,
- Often, enlargement of the right heart, especially the right atrium, is associated with a range of *arrhythmias.*
- For the prevention of disastrous outcomes, *treatment is necessary*. Smaller ASDs impose less burden on the heart and might be closed spontaneously; however, larger ASDs cause a significant burden on the heart leading to unwanted consequences which mandate treatment.
- Some *neurologic complications* might occur during the process of the disease due to particulate or air embolization. For example, paradoxical emboli or rare desaturation episodes may lead to aura, migraine headaches, or even transient ischemic events in the central nervous system.

Diagnosis of ASD

In ASD patients, the process of diagnostic workup should aim mainly at the following:

- Presence of ASD,
- Size of ASD,
- Location of ASD,
- The effect of ASD shunt on left and right ventricular function,
- The effect of ASD shunt on pulmonary circulation,
- Any possible associated lesions.

Diagnosis of ASD

Clinical Presentation and the Course of the Disease

The majority of the patients with ASDs are asymptomatic during neonatal and early childhood. Any of the following findings such as slow weight gain, tachypnea, or recurrent respiratory infections during infancy should raise suspicion of an ASD. Most pediatric patients with ASDs are acyanotic; however, very rarely, mild transient cyanosis may happen in the newborn which is due to a right-to-left shunt. In physical examination, the precordium is hyperdynamic. Fixed splitting of the second heart sound is heard through respiratory cycles; the severity of the pulmonary component of the second heart sound

(P2) corresponds with the severity of pulmonary hypertension only if it is present. The diagnosis in this time domain is usually an incidental finding by echo during routine clinical or paraclinical assessment like looking for the origin of an incidental heart murmur or anything abnormal found in chest X-ray or other studies. Untreated adults have more symptoms and signs, especially related to potential pulmonary hypertension. More explanation regarding adult patients with ASD can be found in chapter "Anesthetic Management of Adults with Congenital Heart Disease"—Anesthetic Management of Adults with Congenital Heart Disease (Andrews et al. 2002; Lammers et al. 2005; Geva et al. 2014; Zvaigzne et al. 2014; Le Gloan et al. 2018; Corno et al. 2021).

In a considerable number of patients with *ASD secundum*, the chance of spontaneous closure is high. The chance of spontaneous closure is higher in those patients with smaller size defects and less than 1 year of age; however, increasing age and larger defects (i.e. more than 10 mm) are not favorable for spontaneous defect closure (Abdelkarim et al. 2016; Behjati-Ardakani et al. 2016). Conversely, *sinus venosus ASD* and *ASD primum* nearly always need surgical treatment and have significant hemodynamic consequences. More than one-fourth of all adult patients with congenital heart defects are ASD cases and among them, about 75% are ASD secundum (Warnes et al. 2008; Vasquez and Lasala 2013).

Exercise Intolerance

An uncommon finding in young ASD patients is the occurrence of exercise intolerance. However, with increasing age, in those who have been untreated, the frequency of exercise intolerance increases surreptitiously due to aggravation of pulmonary vascular function. If ASD secundum remains unrepaired, exercise capacity will decrease as much as 50–60% of the predicted values (Geva et al. 2014; Amedro et al. 2018).

Pulmonary Hypertension

Pulmonary hypertension is not a common finding in neonates and young children, but it may present itself more frequently in untreated adults. Increasing age and female gender are two main predisposing factors for the occurrence of pulmonary hypertension in untreated ASD; Down syndrome, sleep apnea, and pulmonary vascular embolic events are other risk factors. Eisenmenger syndrome is seen in 5–10% of untreated adults (Rosas and Attie 2007; Warnes et al. 2008).

Electrocardiography (ECG)

The main ECG findings for ASD include (Fig. 1):

- Tall P wave due to right atrial enlargement; inverted P waves in inferior leads suggest sinus venosus ASD.
- First degree AV block may be seen.
- Right bundle branch block (usually incomplete form) may be seen especially in untreated adults.
- Right axis deviation; if leftward or left superior QRS axis deviation is seen, one should seek for ASD primum.
- Rhythms other than sinus rhythm are not common; however, atrial fibrillation or flutter may occur in adult patients with prolonged disease leading to right atrium enlargement often occurring after 40 years.
- Hypertrophy of the right ventricle (presented in ECG by RSR′ pattern in right precordial leads) may be seen due to pulmonary hypertension (McCarthy et al. 2003; Webb and Gatzoulis 2006; Lam and Friedman 2011; Geva et al. 2014; Zvaigzne et al. 2014; Kloesel et al. 2016).

Chest X-Ray (CXR)

The chest X-ray is often abnormal in ASD; however, normal CXR does not rule out ASD. The most common findings in CXR of ASD patients include (Webb and Gatzoulis 2006; Geva et al. 2014; Zvaigzne et al. 2014; Behjati-Ardakani et al. 2016; Le Gloan et al. 2018):

- Cardiomegaly which is mainly due to dilation of right-sided chambers is best seen in lateral views. However, in ASD primum, dilation of left-sided chambers may lead to cardiomegaly which may be better seen in lateral views.

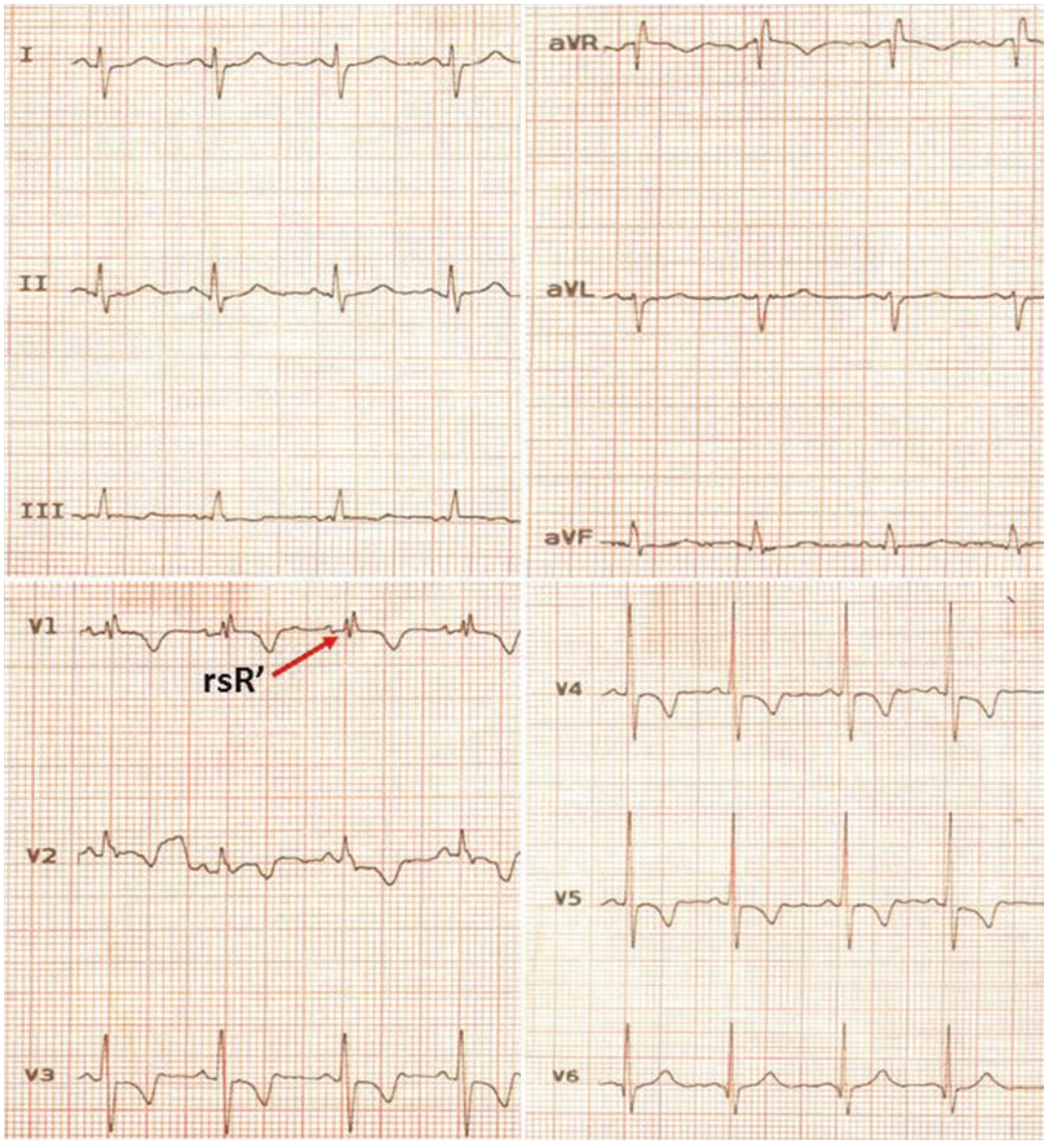

Fig. 1 The rsR′ pattern in lead V1 and right axis deviation are typical characteristics of the atrial septal defect. (Courtesy of Dr. Majid Haghjoo and Dr. Mohammadrafie Khorgami)

- Pulmonary artery trunk and its perfusion domain are enlarged; however, discordance between the main pulmonary artery body and lung fields, leading to a normal appearance of lung fields in the presence of an enlarged pulmonary artery trunk, may be indicative of pulmonary vascular obstructive lesion.
- Small aortic knuckle due to shrinkage of left heart chambers.

Imaging Techniques in the Diagnosis of Atrial Septal Defects

A definitive diagnosis of ASDs may be confirmed via imaging techniques that demonstrate shunting across the interatrial septal defect. Also, any possible right ventricle overload or associated diseases should be detected and diagnosed. These techniques include mainly echocardiography, cardiac computed tomography, cardiac magnetic resonance, and catheterization (Warnes et al. 2008).

Echocardiography

There is no doubt that two-dimensional transthoracic echocardiography with Doppler is the cornerstone for the evaluation of ASD, although not all ASDs can be visualized with transthoracic echocardiography. Echocardiography is the most common diagnostic modality used for all types of ASD during both the primary assessment of the defect and during follow-up visits (Kharouf et al. 2008). The main elements that should be considered in a comprehensive echocardiographic evaluation for ASD mainly include:

- Visualization of ASD with the characterization of its size and location.
- Determining the direction of interatrial flow.
- Right heart examination.
- Pulmonary artery pressure measurement.
- Assessment and estimation of the pulmonary/systemic flow ratio.
- Pulmonary vein flow.
- Left ventricular function.
- Assessment for any associated abnormalities.
- Assessment of all valves.

Post-Intervention assessment of ASD should focus on the following steps:

1. Any possible residual leak.
2. Right ventricle size/function.
3. Septal motion/curvature.
4. LV size/function.
5. Possible mitral valve prolapse (MVP).
6. Pulmonary valve.
7. Right ventricle systolic pressure.
8. Pulmonary artery pressure.
9. Pericardial effusion.

Common Views for Detection of ASD

- Apical four-chamber view.
- Parasternal short-axis view.
- Subcostal views.
- Also, note that not all ASDs can be detected with transthoracic echocardiography.

Other Imaging Studies

Cardiac Magnetic Resonance (CMR)

Cardiac MR (cardiac magnetic resonance) is used both for anatomic assessments and also, for evaluating the hemodynamic effects of interatrial defects; cardiac MR has a great application in sinus venosus ASD. Also, cardiac MR is considered the gold standard in the assessment of RV volume and function and the pulmonary artery and veins. Cardiac MR is the most accurate and fastest data acquisition modality. However, this technology is not usually used before the treatment of ASD secundum and has a limited application before the treatment of ASD primum (Webb and Gatzoulis 2006; Kharouf et al. 2008; Warnes et al. 2008; Geva et al. 2014).

Cardiac Computed Tomography (CT)

For cardiac CT especially when using high-resolution cardiac CT, many great data could be acquired. However, the data gained from cardiac CT are not significantly more than the data gained from cardiac MR. Cardiac CT also poses a high degree of radiation risk exposure and should be considered if serial examinations are needed.

Cardiac Catheterization

Cardiac catheterization studies are not usually indicated for the evaluation of ASDs, However, cardiac catheterization is useful in the following scenarios (Warnes et al. 2008; Geva et al. 2014):

- ASDs going to be closed with percutaneous devices (i.e., ASD secundum).
- To assess any associated anomaly not diagnosed with other non-invasive imaging modalities,
- For the assessment of the coronary system in adults with ASDs.

Treatment

Regardless of age, ASD closure leads to improvements in the course of the disease, with diminished symptoms and improvement in pulmonary vascular disease, pulmonary arterial pressure, ventricular remodeling, and chamber size. Time of repair depends mainly on the type and size of the defect, age of the patient, associated symptoms, associated anomalies, and several other concomitant factors. However, if treatment is delayed, clinical parameters may become exacerbated; therefore, the sooner treatment is done, the better the general outcome and life expectancy. Surgical closure if performed before 25 years old usually leads to a normal life span. Conversely, if ASD leads to severe irreversible PAH and no evidence of a left-to-right shunt, there is no evidence in favor of ASD closure (Rosas and Attie 2007; Engelfriet et al. 2008; Warnes et al. 2008; Yalonetsky and Lorber 2009; Humenberger et al. 2011; Geva et al. 2014; Sachdeva et al. 2020).

Percutaneous closure of *ASD secundum* with sufficient rims is the preferred approach. Cardiac MR or cardiac catheterization is used for a full assessment of *ASD secundum* and any potentially associated anomaly before repair. However, surgical closure is the main treatment in ASD primum and sinus venosus ASDs. Also, surgical closure of ASD secundum is considered when surgical repair/replacement of a tricuspid valve is planned concomitantly or the anatomy of ASD secundum is not appropriate for deploying a percutaneous device (Warnes et al. 2008). In patients with a diagnosis of ASD primum or sinus venosus ASD (confirmed by echocardiography), no additional imaging studies are needed before surgery (Rigatelli et al. 2007; Kharouf et al. 2008; Warnes et al. 2008; Yalonetsky and Lorber 2009; Humenberger et al. 2011; Geva et al. 2014; Abdelkarim et al. 2016).

According to the "ACC/AHA 2008 Guidelines for the Management of Adults with Congenital Heart Disease," ASD closure in adults (percutaneously or surgically) may be considered if the patient meets the following criteria (*Level of Evidence: C*):

- Net left-to-right shunting,
- Pulmonary artery pressure two-thirds of the systemic pressure or less than that,
- Pulmonary vascular resistance is less than two thirds systemic vascular resistance or it responds to pulmonary vasodilator therapy or test occlusion of the defect (Warnes et al. 2008).

Anesthetic Management During Atrial Septal Defect Repair

Anesthesia for Surgical Treatment

A balanced anesthesia plan is preferred leading to both hemodynamic stability and also, the capacity to perform fast-track extubation. Based upon the patient's condition, arterial and central venous monitoring may be indicated. A pulmonary artery catheter is not recommended and does not derive any additional data that can be obtained with transesophageal echocardiography (TEE). Live time echocardiography is usually performed by an anesthesiologist or cardiologist. Antibiotic prophylaxis should be also considered.

Anesthesia for Interventional Treatment

Although sedation may be used during percutaneous device closure of ASD, anesthesia and tracheal intubation are preferred since transesophageal echocardiography is typically utilized used for

defining the correct deployment of the device and ruling out any residual defect. Sedation may be appropriate if intracardiac echocardiography (i.e., ICE) is utilized.

Ventricular Septal Defect

Ventricular septal defects (VSDs) are among the most common congenital heart diseases. It is the most common congenital defect at birth. If those defects that are part of other complex congenital heart diseases are taken into account, VSDs include up to 40% of all congenital heart diseases (Hoffman 1995; Roguin et al. 1995; Hoffman et al. 2004; Penny and Vick 2011; Jortveit et al. 2016; Dakkak and Oliver 2021). VSDs may involve the interventricular septum (IVS) and is often an isolated defect; however, they might be associated with other congenital disease(s) or as a part of complex congenital heart disease such as the following:

- Conotruncal defects.
  - Tetralogy of Fallot.
  - Transposition of great arteries.
  - Congenitally corrected transposition.
  - Double outlet right ventricle.
  - Double outlet left ventricle.
- Left-sided obstructive lesions.
  - Subaortic stenosis,
  - Aortic coarctation,
  - Interrupted aortic arch.

IVS, which is the main site of the lesion, is composed of two parts:

- The inferior segment which is muscular,
- The superior segment which is membranous.

In the majority of VSDs, blood flows through the left ventricle to the right ventricle, leading to a pulmonary overflow, but systemic desaturation is either absent or minimal. Most small VSDs close spontaneously during the first year of life (Hoffman 1995; Roguin et al. 1995) while the larger ones or "multiple VSD" cases usually need intervention. If they remain untreated, the resultant pulmonary overflow causes a sustained increase in pulmonary vascular resistance (PVR), pulmonary hypertension, and finally, shunt reversal and as a result, systemic desaturation ensues. Although spontaneous closure is a common phenomenon in infancy and childhood, it occurs much less frequently in adulthood.

Embryology and Classification of Ventricular Septal Defects

At the beginning of the fifth week, the primeval ventricles start expanding, leading to the development of the apical parts of the future ventricles from the primary heart tube. This phenomenon has a crucial role in the development of IVS with two main parts:

- *Muscular IVS* develops from the bulboventricular flange; the majority of VSDs are located in this muscular component of IVS.
- *Membranous IVS* connects the upper margin of the bulboventricular flange to the anterior and posterior endocardial cushions. In the "developed" heart, membranous IVS is the smaller part of the septum, at the base of the heart, located between the "inlet" and "outlet" parts of the muscular IVS and beneath the right cusp and the noncoronary cusp of the aortic valve. The membranous septum is divided by the tricuspid valve into two parts known as the pars atrioventricularis and the pars interventricularis. The membranous IVS comprises a small portion of IVS; however, it forms an important boundary between the right-sided chambers and the aortic root (Soto et al. 1980; Minette and Sahn 2006; Anderson et al. 2014).

The development of the IVS is discussed in chapter "Cardiovascular System Embryology and Development"—Cardiovascular System Embryology and Development in detail. However, a brief discussion is presented here:

1. Creation of a median ridge known as the muscular IVS, located near the apex of the ventricular floor; the edge of the muscular IVS is concave and free.
2. Height of IVS is achieved by expansion of the ventricles on each side.
3. IVS myoblasts start active proliferation and increase size.
4. Completion of the conal septum as a result of tissue extension, starting from the inferior part of the endocardial cushion up to the top of muscular IVS—these tissues merge with the neighboring portion of the conus septum.
5. Three sources of tissue take part in the closure of interventricular opening and formation of membranous IVS: the *left* bulbar ridge, the *right* bulbar ridge, and the endocardial cushions.
6. The final step is the closure of the opening above the muscular IVS with the development of the membranous IVS and when the interventricular foramen closes completely.

The *primary ventricular septum* or *primary ventricular fold* is produced following the trabeculation of the ventral part of the muscular IVS. However, there is a smooth part on the dorsal wall of IVS, named the *inlet septum*; this nomenclature is used because it is located nearby the AV canals. The *moderator band* or *septomarginal trabecula* is located on the right wall of muscular IVS, between the primary trabeculated fold and the inlet septum. This structure is a firm connection between the muscular septum and the anterior papillary muscle. When the right ventricular chamber expands, the moderator band is formed nearby the AV canal and dorsal muscular IVS. Eventually, a large part of the mature right ventricular chamber is formed by this expansion. However, if this anatomic area expands incompletely, the developing tricuspid part of the atrioventricular canal remains attached to the interventricular foramen, leading to tricuspid atresia and/or other tricuspid valve anomalies (Lamers and Moorman 2002; Gittenberger-de Groot et al. 2005; Togi et al. 2006; Lin et al. 2012; Spicer et al. 2013, 2014; Poelmann et al. 2014; Laura et al. 2020; Annabi et al. 2021; Dakkak and Oliver 2021).

Embryologically speaking, a VSD can develop via one of the following mechanisms:

- Incomplete development of the proximal conotruncal swellings,
- Failed fusion of the muscular and membranous ventricular septa,
- Fusion in merging of the ventral and dorsal endocardial cushions (deficiency in atrioventricular septal),
- Deficiency in the development of the interventricular muscular septum.

VSDs may be classified using an anatomic classification system. Table 2 describes the various classification systems; these systems are based on both embryologic development of IVS and anatomic features of VSD (Soto et al. 1989; Van Praagh et al. 1989; Jacobs et al. 2000; Penny and Vick 2011; Morray 2019).

Pathophysiology of Ventricular Septal Defects

The main determinants of the disease and its pathophysiologic course are:

- The *amount* and the *direction* of the interventricular shunt which is determined by VSD size, the severity of the increase in pulmonary vascular resistance (PVR), and the balance between systemic and pulmonary pressure.
- The degree of *volume loading* imposed on each cardiac chamber (Tweddell et al. 2006; Aguilar and Eugenio 2009; Penny and Vick 2011).

Table 2 Classification of ventricular septal defects

Type of VSD	Mechanism of VSD	Occurrence of the lesion/ clinical outcome	Associated lesions
Nonmuscular VSDs include 3 groups: 1. Perimembranous 2. Outlet type 3. Inlet type			
1. Perimembranous VSD (also known as paramembranous VSD, conotruncal VSD)	Involves the membranous part of IVS; lies in the outflow tract of the left ventricle immediately beneath the aortic valve	The most common type of VSD; approximately 80% of all VSDs	Usually extends into the muscular, inlet, or outlet portion of the ventricular septum
1.1 *Superior border perimembranous VSD; also known as conoventricular VSD* Extends until below the aorta or pulmonary artery or both 1.2 *Posterior border perimembranous VSD* Involves tricuspid valve or its annulus 1.3 *Inferior border perimembranous VSD* Passes over the conduction bundle			
2. Outlet type VSD (also known as subpulmonary VSD, juxta arterial VSD, supracristal VSD, infundibular VSD, subarterial VSD, doubly committed)	*Mechanism and location:* the fibrous continuity that is *between aortic and pulmonary valves* borders the VSD; so, the VSD is located immediately below the pulmonary valve, just inferior to the center of the right coronary cusp	*Occurrence:* account for 6% of all VSDs; more common in the oriental population than in western countries (about 30% in oriental compared to 6% in western populations)	*Associated lesions*: risk of aortic valve regurgitation due to the location of defect just below the right coronary cusp The risk of heart block is really low due to the far location from his bundle
3. Inlet type VSD (atrioventricular canal type) VSD	Located just below the septal leaflet of the tricuspid valve	Accounts for 5–8% of all the VSDs	Straddling AV valve chordae
4. Muscular VSDs			
4.1 Apical *muscular*	Located in the apical muscular part of IVS with multiple apparent channels on the right ventricular side and a single defect on the left ventricular side	*ALL MUSCULAR VSDs account for 5–20% of all the VSDs*	
4.2 Mid *muscular* or central *muscular*	Located in the *mid-muscular* segment of IVS with multiple apparent channels on the right ventricular side and a single defect on the left ventricular side		
4.3 High *muscular*	Located in the upper part of the muscular IVS with multiple apparent channels on the right ventricular side and a single defect on the left ventricular side		
4.4 Swiss cheese *muscular*	Multiple defects in muscular IVS		

However, several secondary factors may also affect the pathophysiology of the disease. They are not universal in all VSD patients; however, they occur in some patients and include:

- Presence and degree of prolapse in aortic valve,
- Presence and degree of obstruction in blood flow through the pulmonary outflow tract or systemic outflow tract (Tweddell et al. 2006; Spicer et al. 2014).

During the early days after birth, the degree of the shunt is not severe even in large size VSD since pulmonary vascular resistance is relatively high in the early days of neonatal life. However, after normalization of the pulmonary vascular system and the resulting drop in PVR, the degree of shunt increases, leading to clinical symptoms and signs including those related to pulmonary overflow and left ventricular hypertrophy. In the minority of neonates, PVR does not drop after birth due to VSD leading to sustained neonatal pulmonary pressure, although this is not the typical clinical history of VSD. Typically, PVR remains low until late childhood or early adulthood in most cases. However, the effect of long-term pulmonary overflow would be increased work of the left ventricle, dilation of the left ventricle, and, if untreated, it will lead to left ventricular failure; add to this problem, the chronic effects of pulmonary overflow and the resulting pulmonary hypertension. The final clinical picture is a change in shunt direction from the left-to-right shunt to the usually irreversible right-to-left shunt pattern. If the disease is still ignored, the effects of long-term increased PVR result in right heart failure leading to final stage biventricular failure associated with irreversible pulmonary hypertension (Tweddell et al. 2006; Penny and Vick 2011; Spicer et al. 2013, 2014).

Diagnosis of Ventricular Septal Defects

Clinical Findings

Signs and symptoms are absent in early life; however, they start to appear at 4–8 weeks of age and somewhat earlier in premature neonates. The main clinical findings in VSD patients mainly include the following (Penny and Vick 2011; Spicer et al. 2014):

General Findings

- Growth retardation,
  - Due to several factors including increased blood flow to the pulmonary vascular bed leading to increased breathing work,
  - Decreased oxygen delivery to the systemic organs since larger amounts of blood flow are directed towards the lungs instead of the systemic vascular bed and other organs than the lungs,

Respiratory Findings

- The effects of increased pulmonary vascular blood flow on large airways may be seen as some degrees of pressure on the tracheobronchial tree leading to signs and symptoms of large airway disease,
- Increased pulmonary vascular blood flow in the microvascular system is associated with decreased free space for small airways in the peripheral lung fields,
- Signs and symptoms of smaller airways diseases like tachypnea, wheeze, and respiratory distress; these clinical findings are due to pulmonary vascular occlusive disease that may be seen even as early as 6–12 months of life, especially in patients having unrestrictive VSD,

Cardiovascular Findings

- Left ventricular hypertrophy (if occurs),
  - Associated with cardiac apex lateral displacement,
  - Hyperactive precordium is a common clinical finding in patients with volume or pressure overload,
- Pansystolic murmur—if found is usually inversely related to the size of VSD,
- Eisenmenger syndrome (i.e., severe pulmonary hypertension).
  - The patient may be cyanotic, associated with clubbing,
  - Usually, the pansystolic murmur vanishes and instead, a loud P2 is auscultated due to contraction of the right ventricle against high pressure pulmonary vascular system,
  - The clinical findings related to Eisenmenger syndrome do not develop until the teenage years,
- Irregular pulses,
  - Maybe seen in a minority of patients having underlying arrhythmias.

Chest X-Ray

Some general findings are seen in CXR of VSD patients and mostly include:

- Cardiomegaly,
  - Left ventricle hypertrophy,
  - Right ventricular hypertrophy,
- Increased vascular markings of the lung fields,
  - In patients with Eisenmenger's syndrome, the vascular markings fade off the lungs,
- Hyperaeration of the lung fields in patients with increased pulmonary blood flow and the effect on small airways, leading to hyperinflation of the peripheral lung fields (Minette and Sahn 2006; Penny and Vick 2011; Spicer et al. 2014).

Electrocardiography

No specific electrocardiographic abnormalities are associated with small VSD, especially in early neonates; however, signs of left ventricular hypertrophy may occur later in life. In addition, signs of right axis deviation and right ventricular hypertrophy are seen especially in patients with pulmonary over-circulation or pulmonary hypertension. A minority of VSD patients may have the right bundle branch block (RBBB) (Fig. 2). Complete heart block may be seen in some (Minette and Sahn 2006; Penny and Vick 2011; Bai et al. 2012; Spicer et al. 2014; Morray 2019).

Cardiac Catheterization

The main objective in evaluating VSDs is to assess pressures over the chambers and in vascular beds especially in the pulmonary system since the closure of a VSD in a patient with supra-systemic pulmonary pressure (Eisenmenger's syndrome) leads to deteriorating pulmonary hypertension and very poor outcome. Also, the complexity and number of "defects" could be accurately assessed with cardiac catheterization. In addition, any associated anomalies like concomitant aortic regurgitation can be evaluated, especially in patients with a subpulmonary (supracristal) VSD (Minette and Sahn 2006; Tweddell et al. 2006; Warnes et al. 2008; Penny and Vick 2011).

Echocardiography

Echocardiography is considered the cornerstone of all diagnostic modalities both in decision making and in the conduction of treatment. The initial echocardiographic assessment of VSD patients should focus mainly on the following aspects, preferably in the following order of assessment (Cao et al. 2011; Penny and Vick 2011; Spicer et al. 2014).

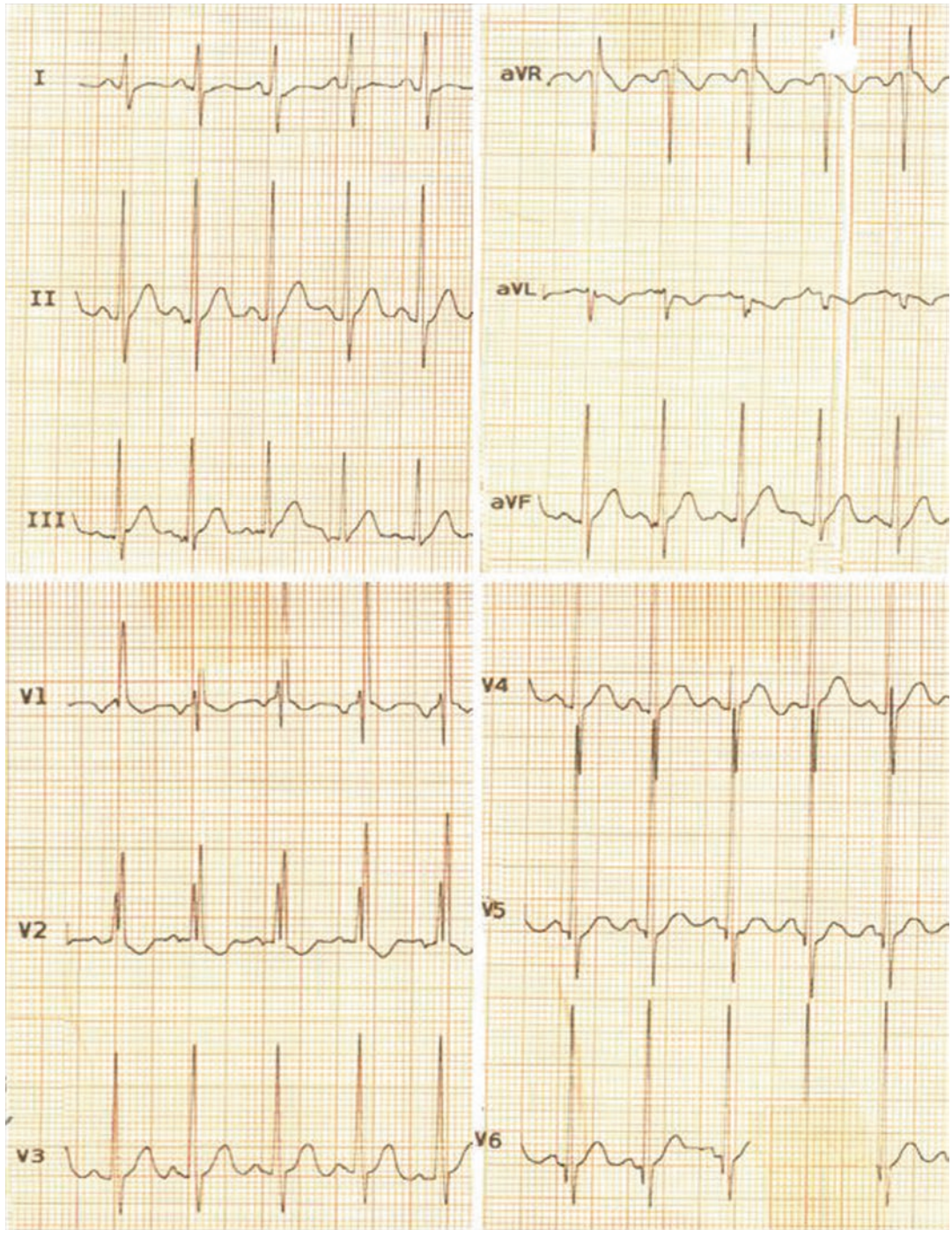

Fig. 2 Ventricular septal defect with pulmonary vascular disease. This ECG shows biventricular hypertrophy and left atrial abnormality. (Courtesy of Dr. Majid Haghjoo and Dr. Mohammadrafie Khorgami)

The initial echocardiographic assessment of the VSD should include the following items:

- Morphology of the defect,
- Malalignment of the defect considering the IVS,
- Size and number of the defect(s),
- Location(s) of the defect(s),
- Gradient across the defect.

Additionally, due to the possible impact of the VSD, the tricuspid valve should be assessed with special focus on the following items:

- Morphology of the tricuspid valve,
- Redundant/aneurysmal tissue in the tricuspid valve,
- Possibility of tricuspid regurgitation.

Right ventricular outflow tract (RVOT) impact from the VSD warrants assessment of the following:

- Hypertrophy of the right ventricle,
- Pulmonary stenosis (PS).

Left ventricular outflow tract (LVOT) should also be assessed due to concerns regarding the following:

- Subaortic ridge.
- Prolapse of the coronary cusps.
- Aortic stenosis/aortic insufficiency.

Mitral valve with special concerns regarding:

- Supra-mitral ring.
- Mitral stenosis/mitral regurgitation.

Also, the following aspects should be assessed:

- Left ventricular size/function.
- Left atrial size.
- Checking for the presence of patent ductus arteriosus.
- Checking for the presence of aortic coarctation.
- Right ventricular systolic pressure and pulmonary artery pressure should be assessed.

In postoperative/post-bypass echocardiographic assessment, it is imperative to assess any possible residual VSD or any possible VSD patch leak. Any residual deficits may require a further surgical reassessment of the defect for successful closure. Also, the function of the left and right sides of the heart and their adaptation to the new post-correction condition should be examined. Post-surgical or intervention, a complete and thorough echocardiographic assessment should be performed (Roberson et al. 1991; Minette and Sahn 2006; Cao et al. 2011; Penny and Vick 2011; Bai et al. 2012; Spicer et al. 2014).

Treatment of Ventricular Septal Defects

The main approach in treatment is *surgical patch closure* of the defect using the atrioventricular

valve approach or semilunar valve approach; ventriculotomy is rarely recommended due to its major sequelae. For muscular defects, especially those that are apical, *transcatheter closure* is used more than other types of VSD due to a very difficult surgical approach. Currently, transcatheter closure is not a routine practice for perimembranous VSDs since there is a considerable chance of heart blocks due to atrioventricular dissociation and some degree of impairments in adjacent valves may occur. With the invention of softer devices and lower profile delivery systems, this method may be used in the future with more frequency for perimembranous defects. Also, in some of the smaller patients with very "difficult" apical VSDs, there is still room for using pulmonary artery banding to prevent irreversible pulmonary hypertension in hope of future corrective surgery. The difficulties in closing muscular apical defects have led some centers to use a hybrid approach by inserting a device in the operating room after surgical exposure of the lesion through a sternotomy (Spicer et al. 2013, 2014; Santhanam et al. 2018; Morray 2019; Aboulhosn and Hijazi 2020; Brown et al. 2021; Cen et al. 2021; Chambault et al. 2021).

Anesthetic Management

A balanced anesthetic with the use of volatile agents and intravenous anesthetics is considered optimal; no conclusive data has been shown to favor any one agent or technique. The use of a pulmonary artery catheter is not indicated as routine monitoring; however, an invasive arterial catheter and the central venous catheter are both commonly used in these patients based on patient condition and co-morbidities. Pulmonary vascular resistance (PVR) should be managed to prevent and increase or decrease blood pressure; increased PVR leads to right-to-left shunting and desaturation; decreased PVR leads to pulmonary over-circulation and increased left-to-right shunting. On-table extubation is used in many centers with attention to PVR and pulmonary arterial pressure; in patients with prolonged defects (especially the adults) or those with associated mixed anomalies more sophisticated assessment should be done before early extubation, especially ruling out any residual defect. Also, RV function, LV function, and pulmonary artery pressure should be assessed after bypass using TEE. Appropriate postoperative pain management is a key issue to address. In patients with a previous history of PA banding, care should be given to control hemostasis in redo corrective surgeries. In patients undergoing device closure, general anesthesia is often the preferred approach, especially when using TEE for the detection of residual defects (Takeuchi et al. 2000; Galante 2011; Twite and Friesen 2014).

Outcome

The overall outcome of children with VSDs is favorable. Jortveit et al. studied 3495 children with VSDs; their overall mortality and/or morbidity rate was very low coupled with a low incidence of arrhythmias (4.6%), aortic regurgitation (3.4%), endocarditis (3.4%), and pulmonary hypertension (0.3%) (Jortveit et al. 2016).

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Tetralogy of Fallot

Clementine H. Vo, Gerald A. Bushman,
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Abstract

Congenital heart disease has only recently evolved within the expertise of the pediatric or cardiac anesthesiologist as pediatric cardiac anesthesiology has become recognized as a discrete subspecialty (DiNardo et al., Anesth Analg 110(4):1121–1125, 2010). Historical attempts to "simplify" the cardiac malformations that may be encountered typically ignored specific anatomic details in favor of slotting the lesions into broad categories such as "cyanotic" or "noncyanotic," often understating the fluidity of said lesion under different clinical circumstances. Early textbooks on anesthesia for the congenital cardiac patient often divided cardiac anomalies in very general ways, pointing out specific memorable features associated with some lesions (Lake, Pediatric cardiac anesthesia, McGraw-Hill/Appleton and Lange, New York, NY, 1993). Although useful in the era where most anesthesiologists did not have significant insight into this subspecialty of pediatric disease, rapid advances in the successful surgical treatment of congenital cardiac disease have been paralleled by accumulation of specific cognitive and technical skills by anesthesiologists dedicated to the care of such patients (DiNardo et al., Anesth Analg 110(4):1121–1125, 2010). Present-day pediatric cardiac anesthesiologists share knowledge of congenital cardiac disease, echocardiography, and the physiologic challenges of catheterization lab procedures with the pediatric cardiologist; the details of surgical technique and management of cardiopulmonary bypass (CPB) with the cardiac surgeon; and the management and expectations of preoperative care and postoperative convalescence (including the management of extracorporeal membrane oxygenation) with the pediatric cardiac intensive care physician. The assessment of a patient with congenital heart disease by the contemporary pediatric cardiac anesthesiologist is a complex synthesis of the anatomic details of a specific cardiac lesion, the patient's status within the natural history of the lesion, consideration of how anesthesia techniques and the operative environment will predictably intrude on the homeostasis of the patient's cardiac physiology, and how those risks might be tolerated and minimized. The author's goal for the next two chapters is not to present an encyclopedic review of the material with inarguable

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advice on anesthesia technique and management. Instead, a contextual presentation including embryology and anatomy, physiology correlated with the anatomy, medical and surgical management, and the natural history of the disease is presented with the assumption that a well-informed practitioner can apply their enhanced knowledge of the cardiac disease in making informed choices regarding anesthesia management.

Keywords

Patent ductus arteriosus · Ventricular septal defect · Pulmonary valve · Pulmonary blood flow · Right ventricular outflow tract

Introduction

Congenital heart disease has only recently evolved within the expertise of the pediatric or cardiac anesthesiologist as pediatric cardiac anesthesiology has become recognized as a discrete subspecialty (DiNardo et al. 2010). Historical attempts to "simplify" the cardiac malformations that may be encountered typically ignored specific anatomic details in favor of slotting the lesions into broad categories such as "cyanotic" or "noncyanotic," often understating the fluidity of said lesion under different clinical circumstances. Early textbooks on anesthesia for the congenital cardiac patient often divided cardiac anomalies in very general ways, pointing out specific memorable features associated with some lesions (Lake 1993). Although useful in the era where most anesthesiologists did not have significant insight into this subspecialty of pediatric disease, rapid advances in the successful surgical treatment of congenital cardiac disease have been paralleled by accumulation of specific cognitive and technical skills by anesthesiologists dedicated to the care of such patients (DiNardo et al. 2010). Present-day pediatric cardiac anesthesiologists share knowledge of congenital cardiac disease, echocardiography, and the physiologic challenges of catheterization lab procedures with the pediatric cardiologist; the details of surgical technique and management of cardiopulmonary bypass with the cardiac surgeon; and the management and expectations of preoperative care and postoperative convalescence (including the management of extracorporeal membrane oxygenation) with the pediatric cardiac intensive care physician. The assessment of a patient with congenital heart disease by the contemporary pediatric cardiac anesthesiologist is a complex synthesis of the anatomic details of a specific cardiac lesion, the patient's status within the natural history of the lesion, consideration of how anesthesia techniques and the operative environment will predictably intrude on the homeostasis of the patient's cardiac physiology, and how those risks might be tolerated and minimized. The author's goal for the next two chapters is not to present an encyclopedic review of the material with inarguable advice on anesthesia technique and management. Instead, a contextual presentation including embryology and anatomy, physiology correlated with the anatomy, medical and surgical management, and the natural history of the disease is presented with the assumption that a well-informed practitioner can apply their enhanced knowledge of the cardiac disease in making informed choices regarding anesthesia management.

For the purposes of precisely delineating cyanotic congenital cardiac disease, it is useful to consider the physiologic substrate of cyanosis as it derives from cardiac (rather than pulmonary) etiologies. Cyanosis or systemic desaturation of arterial blood may be the result of an inadequate amount of pulmonary blood flow relative to systemic blood flow, that is, a pulmonary to systemic flow ratio (Qp/Qs) of less than one (Waldman and Wernly 1999). Alternatively, cyanosis may result from abnormal mixing within the cardiac chambers of fully saturated pulmonary venous blood with desaturated systemic venous blood and access of the desaturated admixture to the arterial circulation (Tharakan 2011). Desaturation of arterialized blood due to intracardiac mixing is largely independent of the pulmonary to systemic flow ratio, and the Q_p/Q_s of a mixing lesion may be greater than one if there are intracardiac septal defects and a suitably low pulmonary vascular resistance compared to systemic vascular resis-

tance. The eponymous representatives of these different cyanotic anomalies are tetralogy of Fallot (TOF) and transposition of the great arteries (TGA). They are a part of the broader group of cardiac anomalies due to conotruncal malformation that also includes double-outlet right ventricle (DORV) and truncus arteriosus.

Case Presentation

A 6-month-old infant presents for surgical resection of a recently diagnosed intra-abdominal tumor believed to be a Wilms' tumor. The patient also has tetralogy of Fallot. Surgical correction of the cardiac defect has been deferred because the patient has had stable arterial saturations of about 92% without overt hypercyanotic episodes.

What is TOF and when is it typically repaired? What affects the timing of repair?

Should this patient have definitive cardiac repair prior to laparotomy?

What are the cardiac findings to investigate prior to undertaking laparotomy? How are the cardiac findings relevant to the patient's perioperative course?

What are the management issues of the induction and maintenance of anesthesia for laparotomy?

What is the importance of preoperative or intraoperative beta-blockade?

What postoperative risks should be anticipated and how should they be minimized?

Embryology and Anatomy

The embryologic substrate of tetralogy of Fallot (TOF) is abnormal conotruncal development (Rudolph 2009). Normally, fetal ventricular partitioning occurs as the muscular septum grows from the floor of the ventricular chamber and the membranous septum develops from the atrioventricular valve apparatus and the bulbar ridges. The bulbar ridges of the bulbus cordis and the truncal ridges of the truncus arteriosus grow toward each other in order to form the primitive aorticopulmonary trunk, which has a spiral septation (Fig. 1). The coordination of the further development of the bulbus cordis with normal spiraling and septation of the primitive truncus results in a right ventricular outflow tract (RVOT)

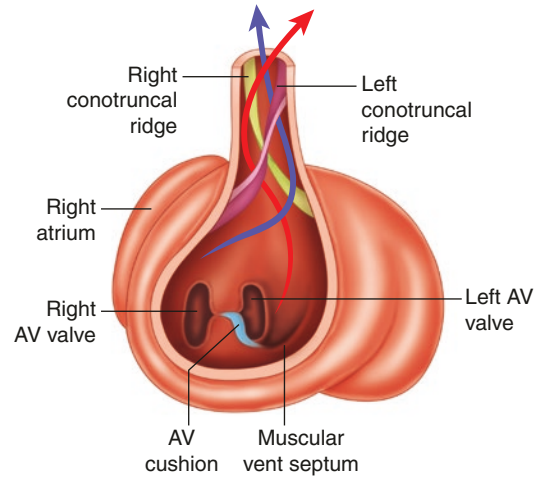

Fig. 1 Conotruncal spiraling

in unobstructed continuity with the pulmonary artery, and the left ventricular outflow tract in unobstructed continuity with the aorta, with the membranous and muscular portions of the ventricular septum intact. In TOF, asymmetric fusion of the bulbar and truncal ridges during maturation causes anterior malalignment of the aorticopulmonary septum. Further abnormal conal rotation contributes to anterior malalignment of the ventricular septum and an aortic position that overrides the ventricular septal defect (VSD) rather than being committed to the left ventricular outflow tract (Bartelings and Gittenberger-de Groot 1991). By week 7, the process is complete, and the anatomic substrate for three of the four components of tetralogy of Fallot is present: hypoplasia of the right ventricular outflow tract with pulmonary valve (PV) stenosis, a ventricular septal defect (VSD), and an aortic position overriding the VSD. The development of right ventricular hypertrophy (RVH) is often a postnatal event and depends on the degree of fixed and dynamic obstruction of the right ventricular outflow tract (RVOT) and pulmonary valve (PV) (*Allen*) (Fig. 2). Tetralogy of Fallot's conotruncal maldevelopment can often be blurred with double-outlet right ventricle (DORV), in which the extent of aortic override and position of the ventricular septal defect can classify a lesion as being DORV—"Tet type" (Spaeth 2014). The specifics of DORV will not be detailed in this chapter, but it is important to note that there exists

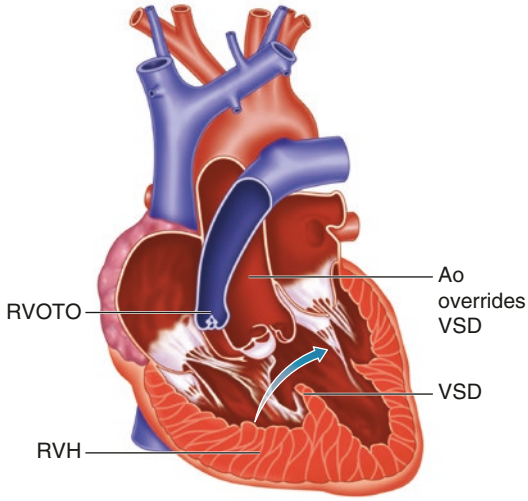

Fig. 2 Features of TOF

much variability in conotruncal abnormalities and both surgical and anesthetic approaches may differ.

Uncomplicated TOF

Presentation and Anatomic Correlation

A neonate born with TOF typically has three of the four important anatomic components: a perimembranous VSD, an anteriorly malaligned right ventricular outflow tract with stenosis or hypoplasia of the pulmonary valve or main pulmonary artery, and an overriding aorta that is positioned over the VSD rather than more posteriorly related to the left ventricular outflow tract (Anderson and Weinberg 2005). Often, depending on the degree of obstruction to pulmonary blood flow by the hypoplastic portions of the RVOT, a neonate demonstrates little or no cyanosis and may have chest X-ray evidence of cardiomegaly and increased pulmonary vascular markings, consistent with the findings of a ventricular septal defect. This is especially true in the first few days of life when the ductus arteriosus is likely sufficiently patent. Any signs or symptoms referable to the VSD and pulmonary overcirculation regress over weeks to months, and the patient begins to develop the fourth component of TOF, right ventricular hypertrophy, due to the progressive volume and pressure overload.

It is useful to consider the RVOT obstruction as having two physiologic components that correlate with the anatomic details present in the patient. The RVOT obstruction due to dysmorphology of the pulmonary valve or pulmonary artery has a "fixed" restrictive effect on pulmonary blood flow. That is, the obstruction does not significantly change with the loading or contractile conditions of the RV, the heart rate, or the systemic afterload. As the neonate grows, the restriction to pulmonary blood flow by the fixed obstruction becomes more important, and desaturation occurs as the Qp/Qs decreases below one.

Because of the small, anteriorly malaligned RVOT, the "dynamic" obstruction typically occurs at the infundibulum of the right ventricle (Little et al. 1963). Unlike the fixed obstruction that may be present at the pulmonary valve or pulmonary artery, the dynamic obstruction of the RVOT varies with the contractile state, the preload and afterload conditions of the right ventricle, and with the heart rate. While the fixed RVOT obstruction tends to worsen according to the degree of obstruction relative to the infant's size and decreases in arterial saturation are gradual, the dynamic obstruction at the infundibulum reflects progressive concentric hypertrophy and disorganization of the myofibrils of the infundibulum unrelated to the infant's growth (Geva et al. 1995). Dynamic RVOT obstruction worsens with time irrespective of growth (Soto et al. 1981). The hypercyanosis seen during a "Tet spell" is episodic and related to specific situations associated with tachycardia, decreased preload and/or afterload, and/or increased contractile performance of the RV.

Under quiet conditions, infants normally do not experience the decreases in preload or afterload that would precipitate a "Tet spell." However, crying is the behavior that most frequently causes the infant to become tachycardic with increased cardiac output (CO) precipitating hypercyanosis. Relative to the increased CO, the amount of

blood that can traverse the RVOT is decreased, and the right-to-left shunt at the ventricular septal defect increases. The Qp/Qs during these episodes decreases, and the proportional decrease in arterial oxygen saturation (SaO_2) correlates with the relatively decreased pulmonary blood flow. In addition, the aortic valve overriding the VSD is in excellent position to receive systolic blood flow ejected from the right as well as the left ventricle as the impediment of RVOT obstruction (analogous to "mechanical" pulmonary vascular resistance) approaches systemic vascular resistance. The mainstay of medical management in such patients prior to operative repair is beta-blockade with propranolol, which reduces the incidence and severity of infundibular spasm (Thapar and Rao 1990).

As RVOT obstruction becomes important in infancy in TOF, failure to thrive is rarely seen, and if present, noncardiac causes should be considered. It is much more common for these infants to be in the upper percentile of weight for their length and age, as the usual reaction from parents to the hypercyanosis that occurs with crying is to placate the infant with additional feeding.

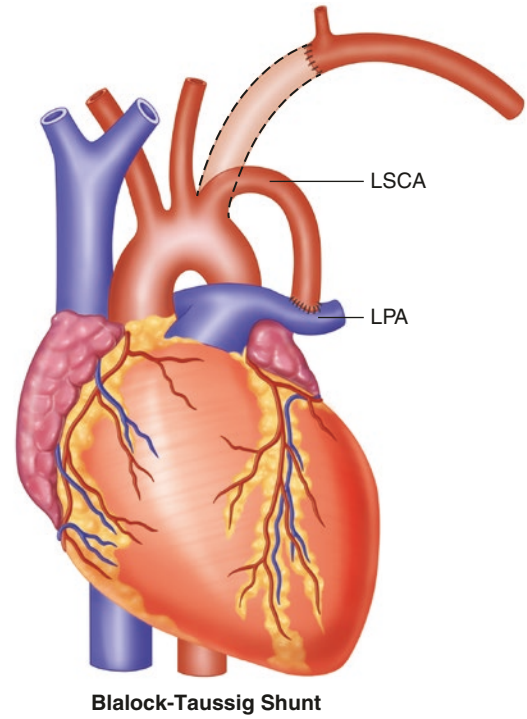

Fig. 3 Classic BT shunt

Historical Therapeutic Approaches and Outcomes

The concept of surgical palliation of TOF originated with the observation that patients with cyanotic heart disease who also had a patent ductus arteriosus (PDA) outlived cyanotic patients without a PDA. Beginning in 1944, a classic Blalock-Taussig shunt (BTS) was performed in selected toddlers and children to relieve cyanosis (Blalock and Taussig 1945). Smaller children with the most severe manifestations of TOF usually did not survive infancy to undergo palliation.

The classic BTS is an end-to-side anastomosis of the subclavian artery to the pulmonary artery allowing a stable source of pulmonary blood flow that grows with the patient (Fig. 3). Patients typically remained somewhat desaturated. Manifestations of chronic hypoxemia and polycythemia were increasingly seen in long-term survivors of initial palliative shunting; however, the paroxysms of hypercyanosis that the patient typically attempted to relieve by squatting were resolved (Hansen et al. 1995). In that era, complete surgical repair was not contemplated. Attempts at evolving the concept of a systemic-to-pulmonary shunt that would provide more durable relief of cyanosis resulted in the Waterston shunt, which created an aortopulmonary window from the ascending aorta to the right pulmonary artery, and the Potts shunt, which created a window from the descending aorta to the left pulmonary artery (Pickering et al. 1971; Levy and Blalock 1939) (Fig. 4). These shunts provided torrential, but often one-sided blood flow to the pulmonary circulation (Trucoone et al. 1974; Newfeld et al. 1977).

When Clarence Walton Lillehei initiated the era of complete repair of TOF in 1954, the VSD was closed, and the RVOT was reconstructed utilizing extracorporeal circulation (Lillehei et al. 1955, 1986) (Fig. 5). Many of the patients were survivors of Waterston and Potts shunts, and a high incidence of pulmonary artery distortion and pulmonary vascular disease (often in one

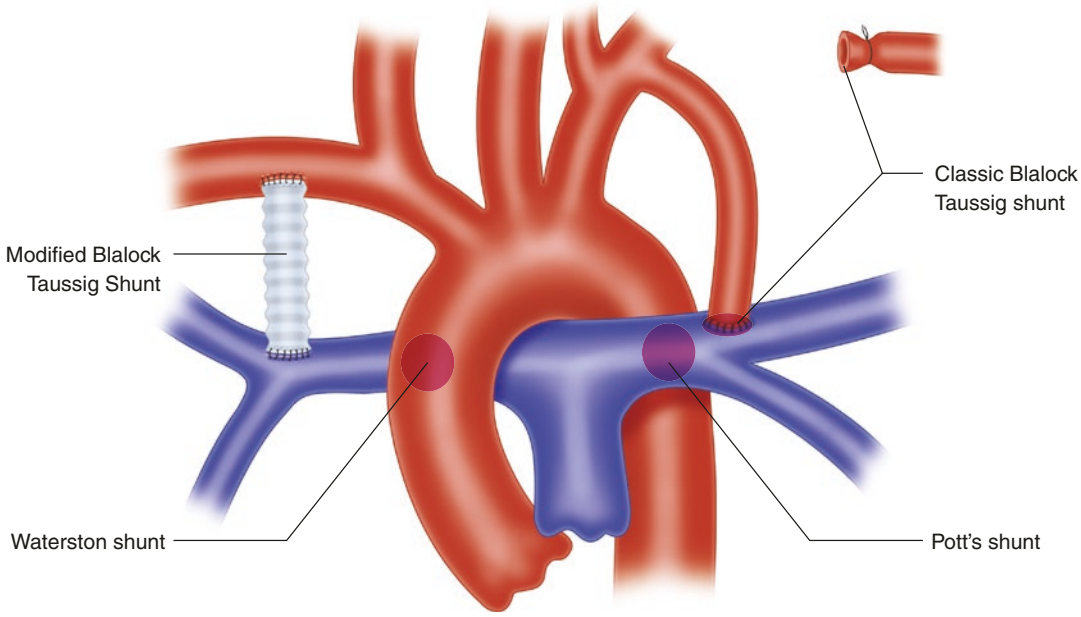

Fig. 4 Types of shunts

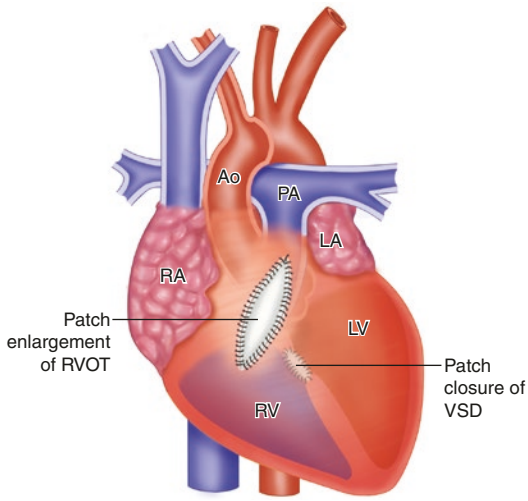

Fig. 5 TOF repair

lung) was appreciated (Trucoone et al. 1974). The potential of complete repair obviated the notion that the shunt was permanent palliation, and further modifications of the systemic-to-pulmonary artery shunt reflected the consideration that as a palliative strategy preceding complete repair, the temporary augmentation of pulmonary blood flow should be controlled rather than excessive, and the pulmonary artery architecture and growth potential should be undamaged by the shunt (Lamberti et al. 1984). The contemporary refinements of the early shunts are the modified Blalock-Taussig shunt (MBTS), a Gore-Tex tube from the right innominate or subclavian artery to the right pulmonary artery, and the central shunt, a Gore-Tex tube from the ascending aorta to the main pulmonary artery (Fig. 6). When palliation is required, a stable and predictable augmentation of pulmonary blood flow can be accomplished by carefully choosing the size of the shunt and the placement of the proximal anastomosis. The longevity of the shunt is less a concern as complete repair can now be undertaken at low risk on most patients during infancy (Stephenson et al. 1978).

Early outcome data from the first several decades of complete TOF repair showed the likelihood of survival, and an acceptable long-term result was closely related to how completely the right ventricular outflow tract obstruction was relieved (Bahnson 1982). Complete surgical excision of the pulmonary valve was common, and the right ventriculotomy was extended to the apex of the heart to fully resect the infundibulum

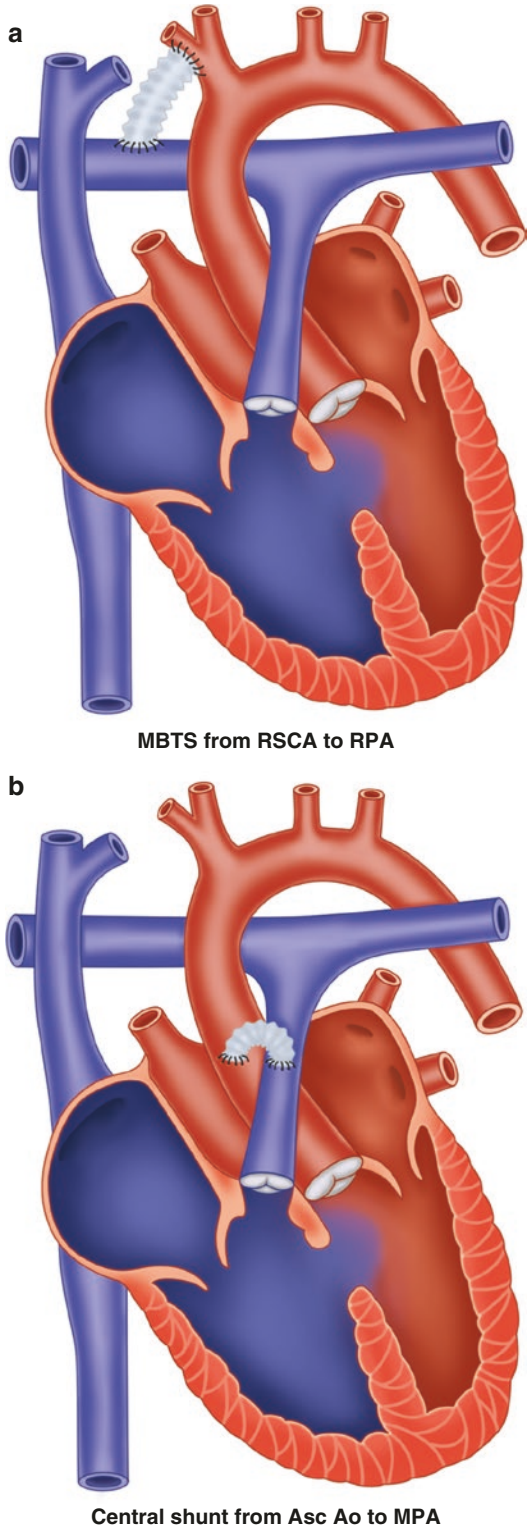

Fig. 6 MBTS (**a**) and central shunt (**b**)

and any prominent right ventricular muscle bands (Kirklin and Karp 1970). Acute pulmonary insufficiency associated with this approach is initially well tolerated in most patients. It took many decades for long-term outcome data to demonstrate that right ventricular dysfunction and failure (and the associated left ventricular dysfunction from septal shift), tricuspid valve insufficiency, and severe ventricular arrhythmias as a result of ventricular hypertrophy and dilation were the consequences of the aggressiveness in managing the RVOT in the original complete repair (Garson et al. 1979).

Nonetheless, despite the early application of surgical and anesthesia efforts and perfusion technology in the 1950s through the 1970s, there are many adult survivors of palliative shunting followed by complete repair of TOF. As the incidences of pulmonary vascular disease, branch pulmonary artery stenosis due to the shunt, right ventricular failure with occasional left ventricular failure, and chronic arrhythmias are now well defined in this adult cohort, contemporary surgical repair is aimed at not only excellent short-term survival but also intact and functional long-term survival, even at the expense of occasional late reintervention to optimize the RVOT (Myers et al. 2014; Cuypers et al. 2014).

Contemporary Surgical Management and Outcomes

Tetralogy of Fallot is typically diagnosed in the neonatal period or early infancy. Although prenatal diagnosis is possible, it is not common for the lesion to be identified before birth unless there is also pulmonary atresia or hypoplastic right heart syndrome. The presentation is related to the amount of fixed obstruction of the RVOT and cyanosis, and a crescendo/decrescendo systolic heart murmur with a diminished pulmonary component is common. Chest X-ray eventually shows the pathognomonic boot-shaped cardiac silhouette due to right ventricular hypertrophy, and an electrocardiogram (ECG) shows RV hypertrophy and exaggerated

right axis deviation for age during infancy (Allen et al. 2013). The anatomic diagnosis is confirmed by echocardiography, and only in the case of specific complex variations would catheterization and angiography be indicated.

Because of the common availability of echocardiography, infants are usually diagnosed early, before severe manifestations of infundibular hypertrophy and paroxysms of hypercyanosis are evident. As dynamic obstruction progresses, medical management with propranolol is frequently used to reduce hypercyanosis, while preparations for surgery are undertaken.

Timing of Surgery

The timing of corrective surgery for uncomplicated TOF is somewhat controversial (Steiner et al. 2014; Barron 2013). Excellent results have been obtained in some centers by operative repair in the first few months of life prior to the development of significant cyanosis, justifying the approach with the argument that the time the infant is chronically and episodically hypoxemic is minimized by early repair (Tamesberger et al. 2008; Hirsch et al. 2000). Although fixed obstruction is reliably addressed in the neonate or young infant, hypertrophy of the disorganized myofibrils of the infundibulum may still occur after early repair and lead to early reintervention (Kaza et al. 2009). Some centers have even begun to opt for elective neonatal repair; however, outcome in these neonates who are repaired as early as less than 30 days old has not been consistently positive. There was a significantly higher morbidity and mortality rate in these patients than in those who were repaired in the mid-infancy age group (Steiner et al. 2014). More commonly, repair is undertaken when cyanosis and hypercyanosis become more severe, typically at 6–12 months of age.

Surgical Technique

Closure of the VSD in TOF is usually straightforward, and the use of a pericardial or synthetic patch is standard. Contemporary surgical techniques of RVOT reconstruction have evolved over time and now reflect a refined understanding of the long-term consequences of previous efforts at completely relieving RVOT obstruction (Vida et al. 2014; Bacha 2012; Karl 2008). Although acute pulmonary insufficiency is well tolerated, the eccentric hypertrophy that occurs in the RV due to chronic volume loading often has clinically important long-term sequelae (Fraser 2015). Because the regurgitant fraction of the RV decreases with increased heart rate associated with activity, the adverse impact of RV dilation on RV function may be clinically subtle until the RV is severely dysfunctional, especially if the tricuspid valve remains competent (Borowski et al. 2004). The most common late surgical reintervention in patients who have had previous repair of TOF is to place a functional valve into the pulmonary position to protect the RV from further long-term effects of pulmonary insufficiency (Babu-Narayan et al. 2014; Quail et al. 2012). Somewhat less common is reintervention to relieve RVOT obstruction resulting from recurrent infundibular hypertrophy or progression of native pulmonary valve stenosis (Yoo et al. 2012).

Institutional preferences for transatrial resection of the infundibulum in selected cases versus routine right ventriculotomy exist (Hoohenkerk et al. 2008) (Fig. 7). Bicaval cannulation and aortic occlusion are required for each. In either approach, care is taken by the surgical team to evaluate the RVOT, size of the pulmonary annulus and the morphology of the pulmonary valve, and the sizes of the main and proximal branch pulmonary arteries and create an individual surgical plan for each patient. If a ventriculotomy is required for infundibulectomy in a patient with an adequate pulmonary valve annulus, it is limited to the sub-annular infundibulum and not extended to the apex of the RV (Bacha 2012). Depending on the appearance of the pulmonary valve, one or two leaflets may be left intact if they are not severely dysplastic because some pulmonary valve competence (even if it is associated with mild obstruction) is of both short-term and long-term value in preserving RV function (Vida et al. 2014). If aggressive RVOT resection extending across the annulus with total resection of the

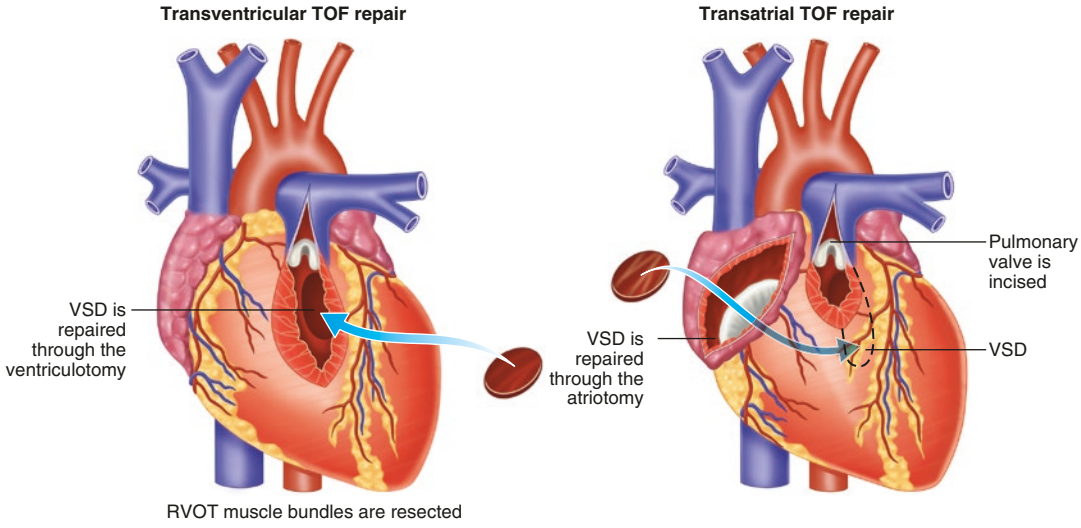

Fig. 7 Transventricular and transatrial repair

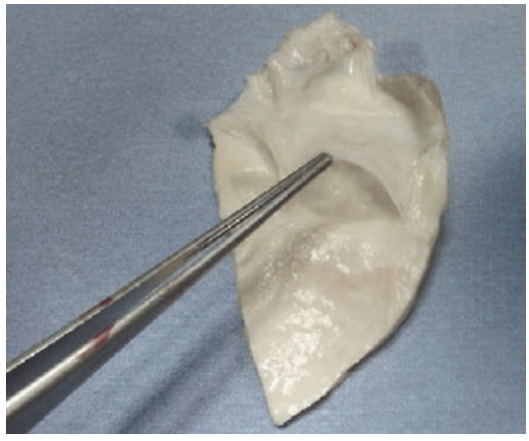

Fig. 8 Homograft monocusp (Mulinari et al. 2008)

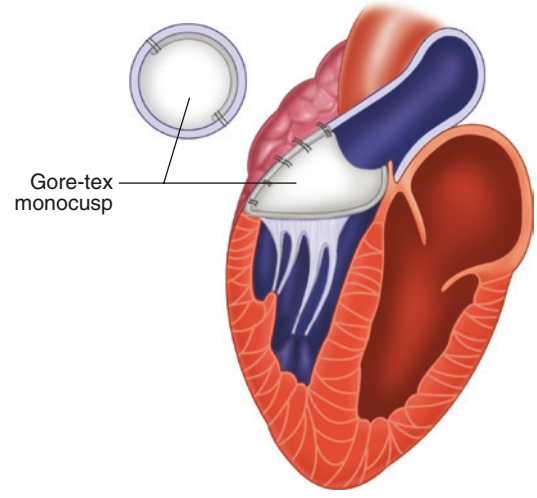

Fig. 9 Gore-tex monocusp

pulmonary valve is required, a monocusp valve (usually homograft) may be incorporated into the RVOT patch leaving a nonautologous valve leaflet in the pulmonary position (Chiappini et al. 2007) (Fig. 8). This technique provides the RV with some protection by reducing pulmonary insufficiency in the postoperative period. Although the longevity of the homograft pulmonary monocusp is limited, its use seems to be associated with a more benign postoperative course. Some authors advocate creating the monocusp from Gore-Tex for increased durability (Turrentine et al. 2002) (Fig. 9).

Natural History of Operative Correction

The natural history of patients following TOF repair is primarily related to the outcome of the RVOT. With the improvement in the surgical techniques in the last 60 years, the incidences of left ventricular failure and pulmonary vascular disease have significantly decreased (Cuypers et al. 2014; Alexiou et al. 2001; Burchill et al. 2011; Lindsey et al. 2010). The VSD repair seems

to not be a long-term issue. The typical ECG of a postoperative TOF patient often shows right bundle branch block or conduction delay from the placement of the VSD patch, but progression to heart block is rare. Ventricular arrhythmias, when they occur, may be suggestive of morphologic changes of the right ventricle late after repair and indicate the need to reexamine the patient's hemodynamics. In the eccentrically hypertrophic dilated RV, arrhythmias are associated with a change in right ventricular geometry, but coronary perfusion and RV ischemia are not an issue. The normal preload/stroke volume relationships are maintained but at larger end-systolic and end-diastolic volumes, primarily due to chronic pulmonary insufficiency from surgery (e.g., transannular patch). In contrast, in the concentrically hypertrophic RV, arrhythmias may be indicative of increases in RV wall thickness and stress that threaten coronary blood flow to the endocardium. In the normal low-pressure RV, right coronary blood flow to the RV endocardium occurs in systole and diastole, but when the RV systolic pressure increases in response to obstruction, the coronary artery flow pattern occurs mainly in diastole (as in the normal left ventricle). The reduced compliance of the concentrically hypertrophic right ventricular chamber also increases the preload dependence of the right ventricle, that is, decreased end-diastolic volume is associated with severe decreases in stroke volume. Otherwise, the relationship between stroke volume and preload is flattened with increased end-diastolic volumes being associated with increased end-diastolic pressure, but not stroke volume (Fig. 10). The right ventriculotomy that is performed during some TOF repairs further reduces ventricular compliance. While these patients have an overall low rate of perioperative mortality, late sudden cardiac death (SCD) related to deadly ventricular arrythmias remains a concern.

Pulmonary valve replacement is the most common surgical reintervention late after initial repair in patients with TOF (Burchill et al. 2011; Geva 2006). The indications are varied, but most relate to the protection of the right ventricle and limiting its exposure to chronic volume loading

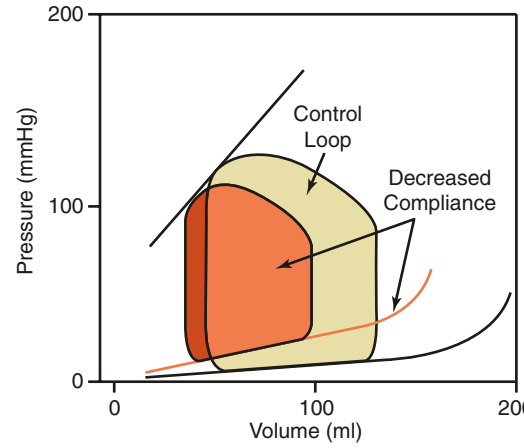

Fig. 10 Compliance curve

(or pressure loading) conditions. Prior to the deleterious late effects on right ventricular function, chronic eccentric dilation of the RV can lead to early tricuspid valve insufficiency if the valve annulus dilates and the valve leaflets fail to coapt. Additionally, as VSDs are often closed via a right atriotomy through the tricuspid valve, any iatrogenic tricuspid valve deficiencies should be addressed. Protection of the tricuspid valve is important for the patient's long-term well-being in that prosthetic valve replacement of the tricuspid valve, although technically simple, is associated with its own unfavorable long-term outcomes (Cheng et al. 2012). Mechanical valves in the tricuspid position have a high incidence of failure from thrombus or pannus formation despite the use of anticoagulation. Biologic valves in the tricuspid position do not require anticoagulation but have limited durability, which is of concern in the pediatric population (Said et al. 2014). Timing of pulmonary valve (PV) replacement may be difficult because symptoms of RV dysfunction, especially associated with pulmonary insufficiency, are subtle until the RV has overtly failed. MRI imaging may be useful in establishing volumetric measurements of cardiac chamber size and regurgitant volumes, and stress testing with echocardiography may reveal subtle presentations of RV dysfunction (Babu-Narayan et al. 2014). Postoperative cardiac MRI surveillance of repaired TOF patients has become more commonplace over the last several years. The timing

of when one begins obtaining MRI assessments after TOF repair remains variable; once performed, however, MRI is performed every 1–3 years depending on the extent of RV dilation found on the last scan (Shin et al. 2016). Asymptomatic patients with an RV end-diastolic volume index (RVEDi) of >150 mL/m^2, RV end-systolic volue index (RVESi) of >80 mL/m^2, or symptomatic patients, independent of their RVEDi, meet the criteria for pulmonary valve replacement (Gune et al. 2019). There appears to be a narrow window of opportune time for PVR, as replacement with RVEDVi of >170 mL/m^2 does not remodel the RV. Furthermore, if PV replacement is delayed until RV function is significantly compromised, the recovery of RV function after valve replacement is not reliable (Hallbergson et al. 2014). If there exists LV dysfunction from ventricular-ventricular interactions, the LV ejection fraction may improve up to 10% post PVR (Tobler et al. 2012).

Although surgical PV replacement is low risk in the older child and teenager, there are the increased risks of repeat sternotomy, including complex surgical bleeding and accidental reentry complications violating the right ventricular outflow tract which is often adhered to the posterior sternal table. Still, the overall risk of surgical PV replacement utilizing cardiopulmonary bypass is very low, and the long-term history of such reconstruction is reliably favorable. Advances in cardiac catheterization intervention techniques over the last decade have made avoiding a repeat sternotomy quite attractive, however. Early outcomes in older children who have had catheter-delivered pulmonary valve into the RVOT have been positive (Cuypers et al. 2014; Cheatham et al. 2015). These lesser invasive techniques were aimed at achieving early intervention for the repaired TOF patient with progressive PI to delay RV dilation. It was initially thought that patients who have had transannular patches were not candidates for percutaneous pulmonary valve intervention (PPVI) as the patch may become aneurysmal, and there is no definitive landing zone (Khambadkone et al. 2007). This arena has progressed to these patients undergoing pre-stenting of the right ventricular outflow tract prior to PPVI to create an adequate landing zone. While this was met with concerns that a pre-stent can worsen PI, migrate, or become fractured, the overall results in patients who meet anatomical criteria are favorable (Cools et al. 2015). Use of percutaneous pulmonary valves continues to evolve, albeit off-label, as the field advances. Because the RVOT of transannular patches can become enlarged, some commercially available valve systems designed for the RVOT may not be sufficient. Larger valve systems originally designed for transcatheter aortic valve replacements (TAVR) as well as newer self-expandable valves have been used in the pulmonary position with some success (Esmaeili et al. 2019; Kim et al. 2020). Coronary anatomy, RVOT position and size, and history of surgical repair play a significant role for a patient's candidacy for PPVI. Unfortunately, the risk of infective endocarditis is relatively high (2%) in these patients compared to surgical replacements; however, overall mid-term outcomes on PPVI in the anatomically appropriate patient remain to have revealed reassuring results (Nordmeyer et al. 2019). Conclusions on long-term outcome and device durability will likely only be available in the coming decade.

Comorbidities

Important comorbidities associated with tetralogy of Fallot include malformations of the multipotent neural crest cells. Derived from the ectoderm germ layer, these cells differentiate into neural cells, connective tissue, pharyngeal arches, parts of the cardiac septum and ultimate bulboventricular/truncal apparatus, and endocrine tissue of thyroid, parathyroid, and thymus glands. DiGeorge syndrome (22q11 deletion) and similar microdeletion syndromes account for some of the frequently observed anomalies seen in 20% of patients with TOF (Lammer et al. 2009). Palatal anatomic abnormalities (such as clefts) and functional abnormalities (such as velopharyngeal incompetence) may be seen (Wyse et al. 1990). Disorders of parathyroid function, renal anomalies, laryngotracheal/esophageal anomalies,

immune disorders from reduced T cell function, skeletal anomalies, and hearing and developmental disorders are frequently encountered in patients with these chromosome disorders. In addition to TOF, the other cardiac anomalies associated with these genetic conditions usually have a substrate of embryologic conotruncal malformation (e.g., ventricular septal defect, transposition of the great arteries, truncus arteriosus, and double outlet right ventricle). Therefore, the potential associations of VACTERL syndrome, DiGeorge syndrome, velocardiofacial syndrome, and CHARGE syndrome should specifically be considered when caring for a patient with TOF (Shprintzen et al. 1981).

Nonsyndromic comorbidities that are important are primarily related to the hematologic consequences of chronic hypoxemia (Tempe and Virmani 2002). A normal hematocrit is frequently seen in cyanotic patients when physiologic anemia is otherwise expected at 2–3 months of age because of increased erythropoiesis. If the infant is nutritionally competent, polycythemia develops over the following months.

The most important consequence of polycythemia in the cyanotic patient about to undergo surgery is platelet dysfunction (Zabala and Guzzetta 2015). Although the platelet count is usually normal, the function of the platelets is diminished. Platelet microparticles are overproduced in cyanotic conditions because of shear forces associated with hyperviscosity of the blood, and there is a higher concentration of circulating immature platelets that have already been activated. Functional stimulation testing of the patient's platelets to an ADP challenge is decreased and inversely proportional to the patient's baseline hematocrit.

Anesthesia Considerations

Most patients with TOF undergo corrective surgery as infants (Kirsch et al. 2009). Many of these patients have a chronic degree of cyanosis, and some also have hypercyanotic spells that may be treated with a beta-blocker. Correlating the parents' observation of cyanosis to the echocardiogram findings of fixed and dynamic obstruction is often useful in predicting how labile the patient's arterial saturation may be under anesthesia, although it is important to note that parents often underreport their infant's episodes of desaturation despite proactively and frequently feeding hoping to minimize the episodes of crying and cyanosis (Sharkey and Sharma 2012).

Although not routinely used by many anesthesiologists caring for infants, there are cogent reasons to consider a premedication in an infant with TOF. If an intravenous (IV) catheter is to be placed prior to induction, the use of a premedication may reduce the likelihood of a hypercyanotic spell during placement (Montero et al. 2015). If an inhalation induction is planned, a sedated infant who is not crying is less likely to "spell" during induction. Although there are some concerns about respiratory depression in a patient with cyanosis, it is the bias of the authors that the benefits of a non-opioid premedication are preferable, and an inhalation induction of anesthesia is routinely performed deferring IV placement until the patient is anesthetized.

The hemodynamic goals during the administration of anesthesia relate to the dynamic portion of RVOT obstruction (Pierce et al. 2012). (There is little the anesthesiologist can do to significantly alter the fixed portion of RVOT obstruction.) In the infant's baseline state, crying and other activities that increase cardiac output are associated with relatively less pulmonary blood flow as more blood is shunted right to left across the VSD and right ventricular blood is ejected out of the aorta in the face of an increasingly obstructive infundibulum. Under anesthesia, the loading conditions of the RV and the patient's systemic afterload are also factors that can be altered by the choice and implementation of anesthesia medications and technique. Decreased venous preloading of the right ventricle can be associated with increased infundibular obstruction and right-to-left shunting. Therefore, dehydration is poorly tolerated, and if the patient does not have an IV preoperatively, the feeding schedule including the administration of clear liquids should be meticulously

planned. Likewise, significant decreases in systemic afterload are associated with increased right-to-left shunting. High doses of volatile agents or the administration of vasodilating intravenous medications such as propofol may be associated with vasodilation and hypercyanosis. Suboptimal depth of anesthesia during important stimulation may be associated with a hyperdynamic response that leads to a "Tet spell".

A wide variety of anesthetic techniques and agents have been successfully used and are not contraindicated as long as the important physiologic goals are met (White 2011). It is of historical interest to note that until it became unavailable, the use of halothane carefully administered was similar to "inhalational beta-blockade" and accomplished the modest decrease in cardiac contractility and heart rate beneficial to TOF physiology (Greeley et al. 1986). The preferential dilation by halothane of the capacitance vessels prior to the resistance vessels could theoretically make the TOF patient unstable, but if the inspired concentration of halothane was carefully limited, hypercyanotic spells during induction were rare. Sevoflurane is successfully used and has significantly less cardiodepression and vasodilation than halothane; "inhalational beta-blockade" does not occur with Sevoflurane. Ketamine has the obvious advantage of maintaining systemic vascular resistance and preload, but the drawbacks of tachycardia and a hyperdynamic state are ~~somewhat~~ inconsistent with our goals of hemodynamic control. Etomidate maintains preload and afterload conditions well, but the lack of depression of cardiac contractile function and heart rate is a disadvantage when the patient is stimulated by endotracheal intubation, unless adjunctive medications are used to blunt the sympathetic response.

While important, the choice of anesthetic agent utilized is not as critical as the approach to anesthetic induction in a TOF patient. Volatile mask induction of an NPO, crying, anxious, difficult-to-mask baby with 8% Sevoflurane is a perfect cocktail for a "tet spell" to occur. The consequences are a further decrease in mixed venous saturation being shunted systemically, worsening acidosis, and a vicious cycle that leads to a deteriorating patient. Anesthesia induction and management should be carefully titrated. As long as preload and afterload are maintained, and heart rate does not significantly increase, SaO_2 of the TOF patient can actually increase during induction from adequate preoxygenation, ventilation, and depth of anesthesia, and maintenance of cardiac output (Tug 2000). It is the authors' opinion that one of the most common reason for a TOF patient to decompensate during induction other than extreme hemodynamic intrusion is airway misadventure. Meticulous and skilled airway management during induction and intubation is as important as the nuances of selecting the optimal induction technique and medications. Beyond the direct effects of hypoxia occurring with poor airway management during induction and intubation, airway obstruction or laryngospasm during poorly managed stage 2 or stage 3 of an inhalation induction is associated with hemodynamic intrusions that are specifically deleterious to the TOF patient (Parker et al. 1999). The hemodynamic effects of acute airway obstruction and the maneuvers required to relieve it are associated with decreases in preload that can precipitate cyanosis. Laryngospasm should be promptly treated with succinylcholine as both high levels of CPAP and propofol can precipitate hypercyanosis. Hypercarbia associated with airway compromise in the unrepaired TOF patient is deleterious primarily because it is associated with sympathetic cardiac activation. Because the pulmonary vascular bed is distal to the fixed obstruction of the RVOT, hypercarbia-induced elevations in pulmonary vascular resistance do not contribute as largely to the right to left shunting. However, efforts to promote adequate oxygenation for what little pulmonary blood flow that does cross the tight outflow tract should still be undertaken.

If a TOF patient has severe desaturation despite a patent, instrumented airway, it must be assumed that pulmonary blood flow is critically decreased. Initial treatment steps should include increasing fractionated concentration of inspired oxygenation. Recall that oxygen content is dependent on the following manipulatable fac-

tors: hemoglobin, arterial oxygen saturation, and arterial oxygen tension. By increasing the FiO_2 and administering a packed red blood cell transfusion (if anemic), one can increase the oxygen content of the mixed venous blood that is being shunted across the VSD. Volume expansion to increase preload, vasoconstriction to increase afterload and decrease right-to-left shunting, and control of inotropic function and heart rate with beta-blockade are acceptable treatments. Alpha-mediated vasoconstrictors are commonly used as both bolus and infusion therapy for hypercyanosis during anesthesia, and although medications such as phenylephrine are effective at first, their effectiveness is limited (Tanaka et al. 2003). If the vasoconstriction also leads to decreased cardiac output as is commonly seen in an infusion of phenylephrine, the concomitant decrease in mixed venous oxygen saturation (SvO_2) results in less impressive increases in SaO_2 over a short time, mimicking "tachyphylaxis." Therefore, it is recommended that phenylephrine use be considered as an effective temporizing measure, while the patient's intravascular volume status is optimized, and beta-blockade considered. Unless the patient is near cardiac arrest, beta-adrenergic agonists should be avoided as increasing contractility can worsen infundibular narrowing (Dinardo and Zvara 2008). Intraoperative beta-blockade in the patient already on propranolol requires caution, and the choice of esmolol, which can be titrated to effect, is advisable (Britt et al. 2014). The ultimate treatment for a hypercyanotic spell refractory to these measures, especially if associated with surgical manipulation of the heart, is to institute cardiopulmonary bypass.

Surgical repair of TOF is considered a low to moderate risk procedure in most institutions, and convalescence is usually uncomplicated. Due to advances in myocardial protection, severe left or right ventricular dysfunction after repair have become less common (Dyamenahalli et al. 2000). Postoperative function of the right ventricle is most related to the intrusion and extent of ventricular muscle resection required to adequately relieve obstruction of the RVOT, and whether it is feasible to leave a portion of the native pulmonary valve in place or alternatively reconstruct the RVOT with a monocusp-type patch (Wells et al. 2002). In contrast to LV function, RV diastolic compliance is poor after repair, and restrictive physiology, even in the absence of residual obstructive lesions, persists in up to 70% of patients postoperatively and requires remodeling to significantly improve (Rathore et al. 2006; Fogel et al. 2012). This RV restriction is due to the increase in right ventricular end diastolic pressure and myocardial stiffness. Postoperative improvement over time in measures of concentric RV hypertrophy is associated with improved RV diastolic function. Risk factors associated with restrictive physiology and RV dysfunction include longer cross clamp and cardiopulmonary bypass times (>100 and >120 min, respectively), transannular patch surgical approach, ventricular hypertrophy, and those with a pre-existing ASD (Sandeep et al. 2019). If RV function is anticipated to be poor postoperatively, some surgeons will leave a small ASD or create a fenestration to provide a "right-to-left pop-off." At the expense of some desaturation, cardiac output is preserved. Echocardiographic examination of the surgical repair is commonly done in the operating room to rule out important residual VSD patch leaks or inadequately relieved RVOT obstruction and to assess ventricular function.

Common postoperative considerations are straightforward. Modest inotropic and lusitropic support may be useful to optimize RV function. Heart block may be seen after repair as the sutures for the VSD patch are in proximity to the conduction system, but it is most commonly temporary unless the surgeon has significantly misplaced a patch stitch. Right bundle branch block usually occurs and is often permanent (Karadeniz et al. 2014). Although malignant ventricular arrhythmias are not common, the postoperative occurrence of junctional ectopic tachycardia (JET) is seen in up to 28% of patients post TOF repair (Ismail et al. 2018). JET may be associated with an exaggerated decrease in cardiac output because the postoperative RV diastolic function is so dependent on adequate loading conditions (Zampi et al. 2012). Interestingly these patients are more stable immediately after surgery and during the 6–10 h required for myocardial reper-

fusion edema to resolve than they are at 12–24 h when JET is typically seen (Andreasen et al. 2008). This underscores the hemodynamic intrusion of ventricular dysmorphology on diastolic function and the importance of paced synchronous or normal sinus rhythm. Temporary atrial and ventricular pacing wires are commonly placed prior to sternal closure to assist managing these conditions (Barker et al. 2013).

Anatomic Variants of TOF

The specific anatomic details of the lesion may determine the timing of surgery. While the degree of RVOT obstruction usually dictates the timing of repair in uncomplicated TOF, other considerations such as size or unusual location of the VSD, additional anomalies such as ductus arteriosus-dependent lesions, severely hypoplastic pulmonary arteries or pulmonary atresia, endocardial cushion defects, coronary artery anomalies involving an anomalous coronary artery crossing the surgical ventriculotomy site, and important noncardiac comorbidities that require urgent surgical intervention may lead the surgical team to perform a palliative systemic-to-pulmonary shunt during early infancy and defer complete repair to a later time.

PDA-Dependent Lesions

Pulmonary Atresia and Critical Pulmonary Stenosis

Some patients with TOF also have atresia or critical stenosis of the pulmonary valve, rendering them PDA dependent for pulmonary blood flow after birth. Normal transition from fetal to neonatal circulation cannot occur, and after stabilization of the neonate with prostaglandin E (PgE), surgical or interventional catheterization treatment is undertaken.

Preoperative evaluation of such complex variants must also carefully assess the morphology of the right ventricle (Yoshimura et al. 2002; Alsoufi et al. 2015). A tripartite right ventricle with an inlet, body, and outlet component is likely to grow and be ultimately usable in a complete repair that includes closure of the VSD. Most centers would attempt to establish antegrade blood flow from the right ventricle to the pulmonary artery by valvotomy or valvectomy as early as possible in the neonate.

The timing and technique of neonatal surgical pulmonary valvotomy has evolved since the 1970s (Humpl et al. 2003). Originally performed in the neonate utilizing "inflow occlusion" or a brief period of cardiopulmonary bypass, the postoperative course of the patient was often stormy and unstable (Odegard et al. 2004). Now it is no longer undertaken as an emergency procedure in response to a neonate becoming cyanotic after delivery, presumably when the PDA constricts. PgE is routinely used to reopen the PDA to relieve cyanosis. Typically, the caliber of an open PDA in a term neonate is 5 mm or larger, so persistent desaturation in the presence of a PDA demonstrated by echocardiography is indicative of moderate elevation of pulmonary vascular resistance. It is common to expectantly observe patients for several days after birth while on PgE in order to detect the beginnings of the normal decline in PVR that will manifest by the SaO_2 increasing to the 90s. Surgical palliation is then undertaken under more stable conditions.

The surgical technique has also undergone refinement. An attempt is made to incise the commonly fused leaflets in an abnormal pulmonary valve, but simple relief of an obstructed valve does not immediately improve the neonate's physiology. The extreme concentric hypertrophy of the right ventricle in these patients makes the postoperative convalescence difficult as the RV is characterized by diastolic dysfunction and significant noncompliance. This leads to right-to-left shunting across an atrial septal defect despite surgical relief of the obstruction at the pulmonary valve level (Schwartz et al. 2013). Sudden dynamic systolic obliteration of the RVOT can also occur, despite alleviation of fixed obstructive components, and is sometimes referred to as "suicide right ventricle" (Fig. 11). A "suicidal ventricle" was originally described in the extremely hypertrophied left ventricle undergo-

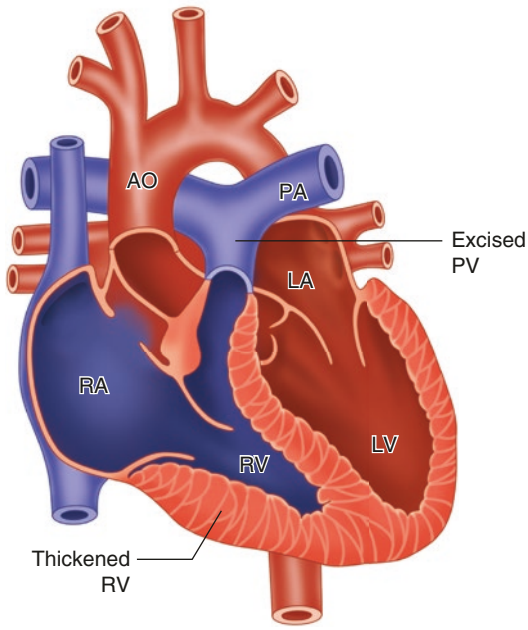

Fig. 11 Suicide RV and right-to-left atrial shunting

ing relief of critical aortic stenosis. A sudden drop in afterload can result in the hypertrophied ventricle to hyperdynamically contract against a reduced force, causing the ventricular cavity to collapse upon itself. Traditional pharmacological resuscitative efforts with epinephrine increase ventricular contractility, worsening this cavitary obliteration. Sudden severe hypotension is especially evident in the patient with an intact ventricular septum, such as with alleviation of isolated critical pulmonary stenosis or radiofrequency ablation of the pulmonary valve in pulmonary atresia/intact ventricular septum (PA/IVS) patients. In those with an interventricular communication, severe cyanosis from right-to-left shunting occurs prior to severe hypotension (Singhi and Kothandam 2015). It is often necessary to leave the patient on PgE after the procedure until diastolic function improves enough to allow adequate antegrade pulmonary blood flow. Placing a modified Blalock-Taussing shunt would provide additional pulmonary blood flow that is independent of RV loading and contractile dynamics; severe cyanosis and decompensation would be mitigated. As RV compliance improves, this additional source of pulmonary blood flow may prove cumbersome, however, as concerns of heart failure or a circular shunt through a regurgitant TOF patch repair arise.

As previously mentioned, timing of complete tetralogy of Fallot repair remains controversial with some centers preferring palliated approaches to neonatal repairs. With advances in interventional cardiology and improved interstage management, deferring a cardiopulmonary bypass run in the neonate may be preferred at many centers and palliation with a PDA stent or modified BT shunt may be opted in the critical pulmonary stenosis or pulmonary atresia patient. The morphology of the PDA varies remarkably amongst congenital heart disease patients rendering technical unpredictability. With introduction of PDA stenting three decades ago, it was recommended that the procedure be undertaken in patients with non-tortuous, uncomplicated ductal courses; however, carotid or axillary arterial access has considerably improved success rates in approaching the complex ductus (Rehman et al. 2018). Complications, including stent migration, ductal spasm with manipulation of the guidewire, and acute thrombosis, with PDA stenting remain uncommon (Alwi 2008). Modified BT shunt placement is another option and, barring moderate to severe desaturation and/or hemodynamic instability, can be done without cardiopulmonary bypass with a side-biting vascular clamp. The decision to proceed with either PDA stenting or surgical palliation lies within the patient's anatomical and hemodynamic candidacy and surgical preference. While there are no major differences in mortality between those who undergo PDA stenting compared to BTS, the former experience shorter ICU stays and more symmetrical pulmonary artery development (Glatz et al. 2018). Although the patient will for a time have two sources of pulmonary blood flow, heart failure is not commonly seen since there are two ventricles to manage the volume load. Corrective surgical repair is often timed with regard to the type of RVOT reconstruction required, especially in the case of anticipated RV to pulmonary artery conduit implantation.

Pulmonary Atresia and Major Aortopulmonary Collaterals

Zachary I. Kleiman and Zoel Augusto Quiñónez

A small subset of patients with Tetralogy of Fallot and Pulmonary Atresia lack adequate pulmonary blood flow via a patent ductus arteriosus (PDA) in utero, and in turn, either develop or persist from embryologic connections between the systemic arterial system and the lung (Fig. 12). These major aortopulmonary collaterals (MAPCAS) originate from the aorta or its branches and supply corresponding lung segments (Fig. 13). Depending on the presence or absence of native pulmonary artery vasculature, some lung segments can be under or over circulated by any combination of flow from the pulmonary arteries and MAPCAS. Systemic pressures in these collaterals can lead to conformational changes resulting in excessive vascular resistance and a decrease in effective pulmonary blood flow over time (Hanley 2006).

Delineating the embryologic origin of MAPCA's continues to be a subject of much academic debate. Rabinovitch et al. theorized that direct collaterals from the dorsal aorta originate from the intersegmental branches present as early as third and fourth week of gestation (Rabinovitch et al. 1981). Due to the development of pulmonary valve atresia at a similar time in utero, they hypothesized that this leads to persistence of these connections between intrapulmonary arteries and intersegmental arteries off the aorta.

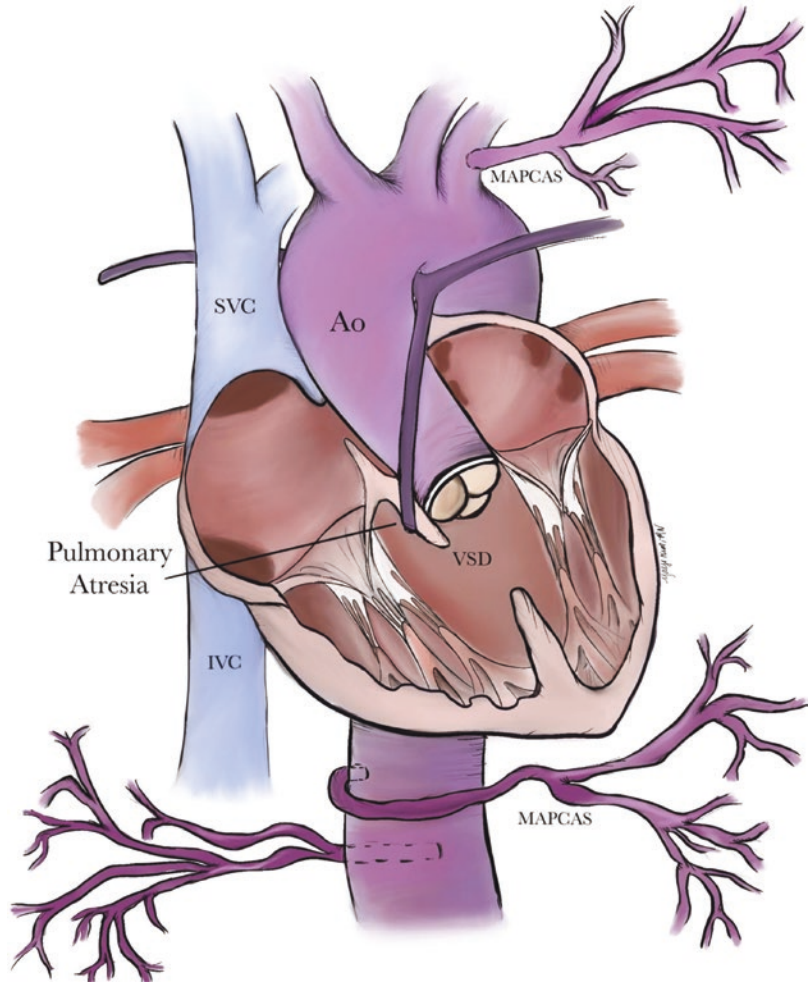

Fig. 12 Illustration of tetralogy of Fallot with pulmonary atresia and aortopulmonary collaterals arising from common sites at the descending aorta and the left subclavian artery to supply various lung segments. (Illustration by Yaeji Kim, RN, Chd_doodles)

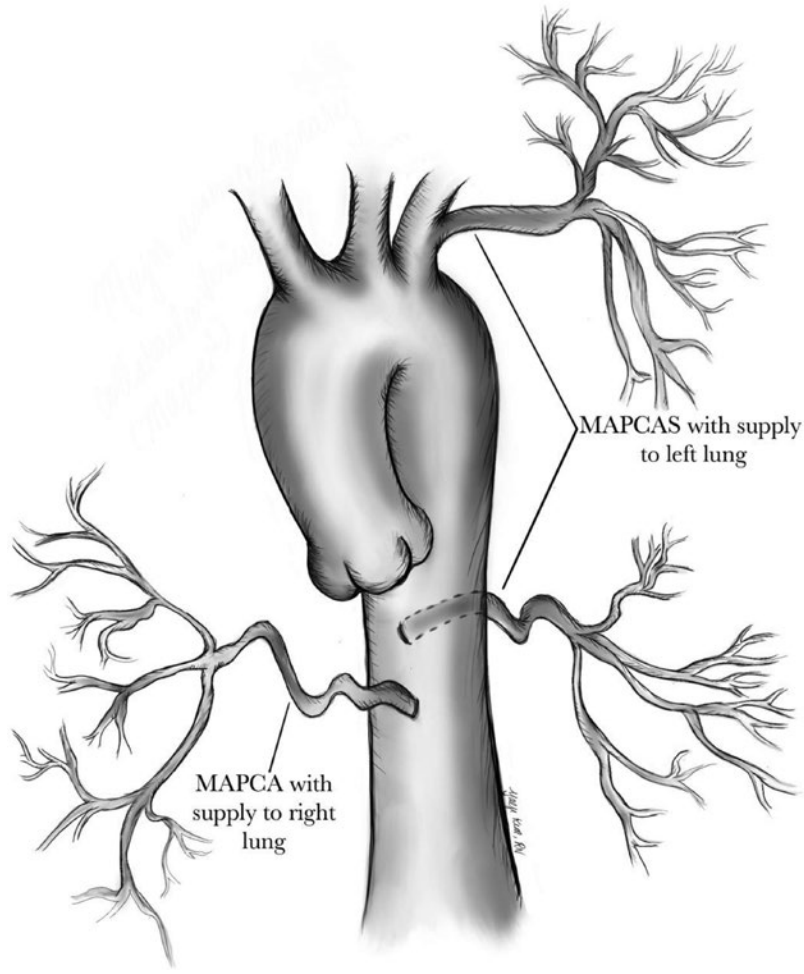

Fig. 13 Illustration of aortopulmonary collaterals commonly seen in Tetralogy of Fallot with pulmonary atresia. Two collateral vessels from the descending thoracic aorta and one from the left subclavian artery supply left and right lung segments. (Illustration by Yaeji Kim, RN, Chd_doodles)

Nørgaard et al. (Nørgaard et al. 2006) postulates that MAPCAS represent dilated bronchial arteries due to similarities in origin, number of arteries present, course and branching pattern, and destination in the lung. Hanley and colleagues (2006) counters by highlighting that MAPCA's and bronchial arteries share a common primordial vascular origin but "environmental factors" lead to either the development of typical bronchial arteries in a heart with anterograde pulmonary blood flow or develop MAPCAs in patients with restricted or absent pulmonary blood flow, as seen in TOF.

MAPCAS can originate from the aorta or its major branches. Adamson and colleagues demonstrate that 88% of MAPCAS (868/1068) originate from the descending thoracic aorta and 52% (560/1068) course rightward. The subclavian artery is the origin in 14% (145/1068) of MAPCAS. The coronary artery can be a source of MAPCAS in 1% of patients. In addition, a right aortic arch with anomalous subclavian artery was a common anatomic variant in patients with 22q11 deletion. Additionally, patients with 22q11 deletion demonstrated no differences in PA size or anatomy (Adamson et al. 2020).

Children with TOF/PA/MAPCAs exhibit cyanosis similar as uncomplicated TOF due to right to left intracardiac shunting. The degree of this cyanosis is dependent on effective pulmonary blood flow from MAPCAs or a PDA. Patients with unrestrictive collaterals will lead to excessive Qp as PVR drops in the neonatal period and will develop signs of LV overload and heart fail-

ure. If MAPCAs are restrictive, the patient will present with cyanosis. Ma and colleagues (Ma et al. 2018) recommend surgical correction via unifocalization by 4–6 months of life before collaterals become irregular, stenotic, and thickened due to high velocity of flow and abnormal shear force. One distinction between TOF and that associated with TOF/PA/MAPCAs is that the nature of the limitation in pulmonary blood flow is fixed rather than dynamic, as in "tet spells." Nonetheless, anecdotally, reactivity of collateral blood flow is seen during interventional and operative procedures that further limits pulmonary blood flow in a way that seems reversible, albeit significant at times.

Diagnosis of patients with TOF/PA/MAPCAs parallels that of patients with other types of congenital heart disease. Pulse oximetry will reveal cyanosis if effective pulmonary blood flow is limited because of a decrease in the left-to-right shunting from the aorta to the pulmonary artery (MAPCA or PDA). Pre and post ductal saturations will be similar due to left to right shunting. Chest radiograph will demonstrate a typical boot shaped heart. Lung fields will appear congested if left to right shunting is in excess or will show a paucity if pulmonary blood flow is restrictive. Echocardiography will show the typical features of TOF. More significant MAPCAs can be detected by their continuous flow pattern. Cardiac catheterization with angiography is the gold standard for delineating MAPCA anatomy, detecting single supply versus dual supply lung segments, and calculating resistance of the distal pulmonary bed (Fig. 14).

A primary approach to the repair of TOF/PA/MAPCAs is to preserve the native pulmonary vascular bed, relieve MAPCA stenosis, and utilize all "raw material" with growth potential in an effort to minimize PVR. Early repair decreases the risk of elevated post repair RV/LV pressure ratio, a primary determinate of mortality. This involves early unifocalization with incorporation of all MAPCAs and native PAs into a neo-PA system, complete biventricular repair with VSD and ASD (if present) closure, and placement of a valved RV-PA conduit to the newly reconstructed PA system (Malhotra and Hanley 2009). Based on the management approach delineated by Ma and colleagues (2018), 85% of patients achieve complete unifocalization in the first 3–6 months of age (Fig. 15). If confluent, diminutive pulmo-

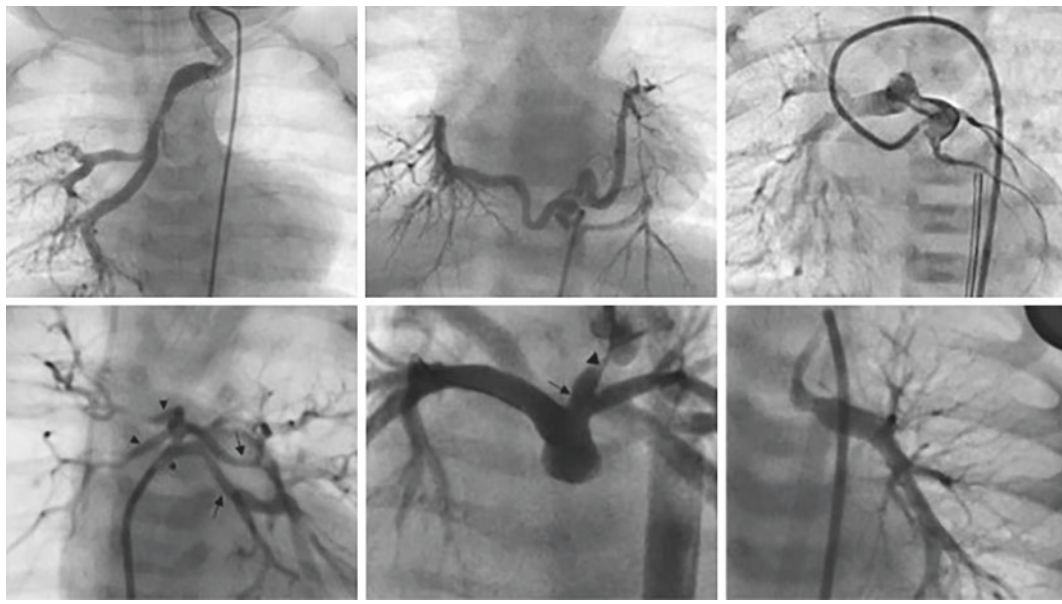

Fig. 14 Examples of major aortopulmonary collateral arteries (MAPCA) and a ductus arteriosus in 6 different patients. (Adamson et al. 2020)

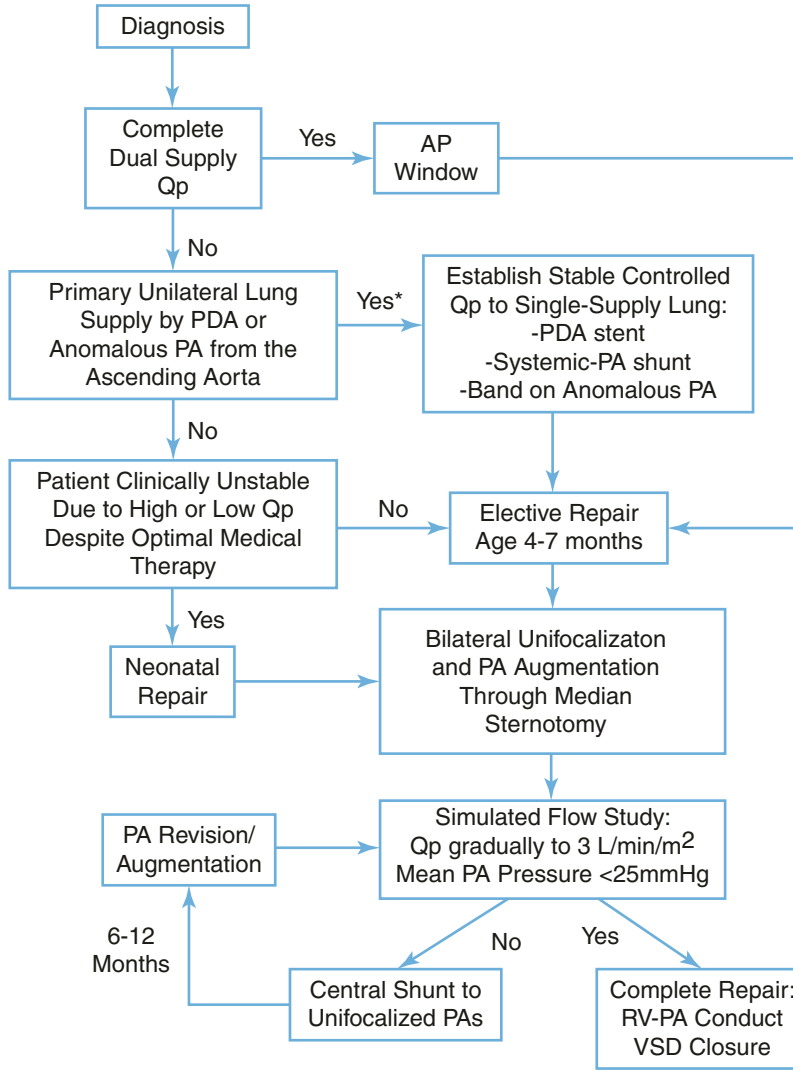

Fig. 15 Lucile Packard children's hospital treatment algorithm for the management of newborns with tetralogy of Fallot and major aortopulmonary collateral arteries. (Ma et al. 2018)

nary arteries exist along with dual supply MAPCAs, an aortopulmonary window may be created to allow for growth of the native PA system. If the patient is clinically unstable due to high or low Qp, unifocalization may be undertaken in the neonatal period.

Decision to close the ventricular septal defect after unifocalization depends on the pulmonary arterial pressures in response to continuous flow from the bypass circuit and through the newly constructed pulmonary arterial tree. After unifocalization of the collateral vessels into the pulmonary arterial system, and while on cardiopulmonary bypass, an arterial cannula is placed proximally in the reconstructed pulmonary arterial system as is a catheter for direct PA pressure measurement. The cardiopulmonary bypass circuit provides flow (up to a cardiac index of 3 L/min) through the newly constructed PA system and a rough estimate of PVR is calculated. If the resistance in the unifocalized system is greater than 25 mmHg, then closure of the VSD is deferred, and a central shunt is placed to allow for further growth. The patient will return after several months for a repeat cardiac catheterization, and subsequently for VSD closure and RV-PA conduit placement (Reddy et al. 1997).

Preoperative assessment prior to surgical correction is paramount to provide an anesthetic that supports blood pressure, oxygen carrying capacity, oxygenation, ventilation, and hemostasis. Patients with TOF/PA/MAPCA can present for surgical correction with varying degrees of oxygenation depending on their Q_p:Q_s ratio. As with other mixing lesions with unrestrictive or mildly restricted left to right shunting, an air-oxygen admixture is preferred for induction with goal saturation of 75–85%, with FiO_2 of 0.21 for those patients with unrestricted left to right flow, to prevent additional pulmonary over-circulation at the expense of coronary perfusion and systemic cardiac output (Quinonez et al. 2018). The anesthesiologist will also have to contend with heart failure symptoms, such as poorly compliant lungs, if pulmonary over circulation is present. Conversely, patients presenting with restrictive collaterals and cyanosis will require an FiO_2 of 1.00 and careful titration of induction to maximize SVR and provide higher perfusion pressure through the pulmonary vasculature. Providers should be prepared to raise the systemic vascular resistance with doses of phenylephrine or vasopressin to maintain sufficient pulmonary blood flow and adequate arterial saturation. This is especially true as surgeons compress collaterals during dissection and can sometimes requires maintaining arterial blood pressure at values well above age-appropriate norms during dissection and before transitioning to cardiopulmonary bypass (Quinonez et al. 2018).

Maintenance of anesthesia follows management principles established for patients with a mixing physiology and either unrestricted, balanced or limited pulmonary blood flow depending on the patient's individual pathophysiology, as described above. At Lucile Packard Children's Hospital at Stanford University, for these procedures that can last between 10–24 h, we prefer a total intravenous anesthetic to avoid compromising pulmonary blood flow with significant drops in systemic vascular resistance (Quinonez et al. 2018). A combination of ketamine, fentanyl, midazolam, or dexmedetomidine infusions are frequently used based on individual provider preference with a heavy opioid base typically greater that 50 mcg/kg of fentanyl. Nondepolarizing paralytic infusions are frequently used, particularly for patients that will be transported to the ICU with an open chest, or that have an expected extended postoperative course due to extensive pulmonary arterial reconstruction or augmentation (Quinonez et al. 2018).

Adequate vascular access, generally achieved either with large peripheral access or percutaneous sheaths, is important due to long procedural times, extended bypass runs, and significant post bypass bleeding. Those patients requiring extensive repair, particularly those repaired in infancy or early life, may require femoral arterial lines due to possible vasospasm or occlusion of peripheral arteries during long, cold bypass runs and the subsequent need for a combination of coagulation products and factors. Central access, typically via the right internal jugular vein, is placed. Patients too small for an internal jugular catheter may require an intrathoracic right atrial line provided by the surgeon prior to weaning from bypass.

Prior to weaning from bypass, the anesthesiologist must ensure the respiratory mechanics are optimized to support adequate oxygenation and ventilation. ICU ventilators with low compliance tubing are sometimes required to allow for precise delivery and monitoring of mechanical ventilation. Frequent suctioning of the airway may be required to clear blood and secretions and can help lower inspiratory pressures to avoid volu- and baro-trauma. Increased blood flow to previously under perfused lung segments can precipitate reperfusion injury characterized by ventilation defects. Wise-Faberowski et al. (2020) documented that 50% of patients undergoing single stage unifocalization developed reperfusion pulmonary edema. Blood products given after weaning from bypass can worsen lung mechanics. Oxygenation and ventilation difficulties are the reasons that delayed sternal closure, or even extra corporeal membrane oxygenation, is required. Lastly, tracheobronchial injury can occur primarily during the significant dissection of the collateral vessels, but also during the repair, or during the post-bypass period (Schulze-Neick et al. 2000).

Thus, any leaks in the ventilatory circuit should raise suspicion for tracheobronchial injury. And in the case of an injury to the airway, broadening of antibiotics may be required per institutional practice.

Inotropes such as dopamine and epinephrine in addition to milrinone, a phosphodiesterase inhibitor, are commonly utilized to augment CO, ensure adequate systemic perfusion, and decrease PVR, although significant inotropic support is generally not required given that unifocalizations are performed with a beating heart and the intracardiac repair is relatively quick. Inhaled iNO is always used to help lower PA pressures to minimize bleeding and optimize V/Q mismatch (Quinonez et al. 2018).

Hemostasis can be very challenging, especially in neonates after bypass times that average 473 min. In addition, prolonged dissections, extensive suture lines associated with the significant pulmonary artery reconstruction, and the newly created shunt or RV-PA conduit are all potential sources of blood loss. Wise-Faberowski et al. (2020) showed that patients undergoing single stage unifocalization required between 110–125 mL/kg of pRBC administration. At many institutions, tranexamic acid is used to decrease clot breakdown. Volume reduced platelets, concentrated fibrinogen, and an anti-inhibitor coagulant complex (FEIBA) are utilized to help stimulate the natural coagulation cascade, to decrease blood product necessity and decrease the risk of further acute lung injury (Rao et al. 2014).

Given the presence of DiGeorge Syndrome (22q11 deletion) in greater than 35% of those with TOF/PA/MAPCAs, intubation of this patient population can be challenging, and additional rescue airway techniques should be available. Placement of a larger endotracheal tube facilitates intraoperative airway clearance and pulmonary rehabilitation post operatively. Due to the preoperative risk of hypocalcemia in these patients, along with significant resuscitation with packed red blood cells, a calcium infusion is often necessary and helpful after separation from cardiopulmonary bypass.

Non-PDA-Dependent Lesions

Absent Pulmonary Valve Syndrome

An uncommon TOF variant is absent pulmonary valve syndrome (Hraska 2005) (Fig. 16). When there is complete absence of pulmonary valve tissue, the proximal pulmonary artery undergoes aneurysmal dilation from the wide-open to-and-fro pulmonary blood flow. The resulting comorbidity is a combination of airway compression by the dilated pulmonary vasculature and tracheobronchomalacia from delayed maturation of the skeletal tracheobronchial tree. Neonates with this anomaly have notable respiratory distress and cyanosis with chest X-ray evidence of barotrauma and air trapping. Intubation and respiratory support prior to surgery are common, and often patients are on significant levels of PEEP or even ventilated in the prone position. Respiratory failure is an indication for neonatal complete repair, which includes the usual components of TOF repair as well as plication of the proximal dilated pulmonary artery. It is not uncommon for repaired infants to return to the operating room for repeat

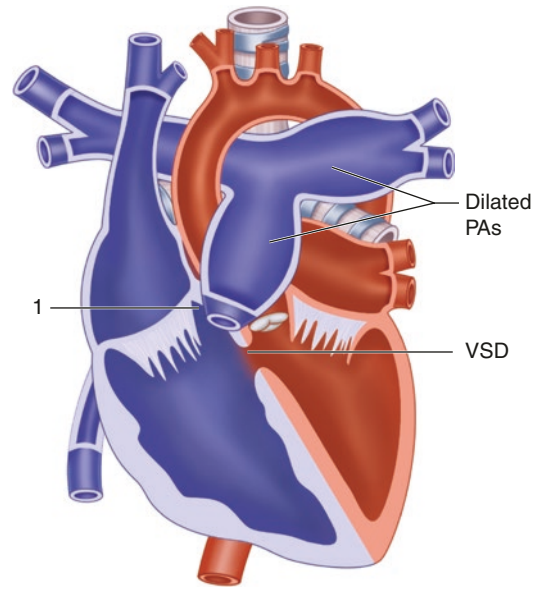

Fig. 16 Absent pulmonary valve syndrome. (1) absent pulmonary valve

plication of the enlarged pulmonary arteries, which can sometimes also compress the SVC, as well as early RV-PA conduit exchange. As with any patient with tracheomalacia, placement of a transesophageal echo probe may worsen airway obstruction. Persistent tracheobronchomalacia is relatively common and may delay ventilator weaning after surgery. Interestingly, absent pulmonary valve syndrome fetuses with a patent ductus arteriosus often die in-utero. Flow from the PDA may create a circular shunt and the massive resultant volume load results in ventricular failure and fetal demise (Edwards et al. 2017).

Coronary Artery Anomalies

Coronary artery anomalies present in up to 10% of patients with TOF, and although they have no impact on the previously discussed physiology issues, they may pose serious implications for the surgeon in accomplishing reconstruction of the RVOT (Dabizzi et al. 1990; Giordano et al. 2017). The most common abnormality is when the left anterior descending (LAD) coronary artery arises from the right coronary artery. If a transannular incision is required in the patient to relieve RVOT obstruction, the LAD may cross in the vicinity of the ventriculotomy site, making the coronary particularly susceptible to injury. As the artery cannot be sacrificed without significant damage to the left ventricle, the surgeon would modify his or her plan to reconstruct RVOT to PA continuity with a conduit, leaving the patient's native RVOT and epicardial coronary artery undisturbed. Although this can be easily done in the infant, the small size or the lack of durability of the conduit that might be used might lead the surgeon to alternatively palliate the patient with a modified BT shunt deferring corrective repair until the patient is larger. Therefore, in every case of TOF, echocardiographic interrogation of the proximal coronary arteries is routinely required for adequate surgical planning. Aortic root or selective coronary angiography to delineate the proximal coronary circulation when it cannot be discerned by echocardiography may be indicated.

Other Anomalies Requiring Palliative Shunting Prior to Complete Repair

Anatomic variants of TOF previously discussed have indicated either the need for a palliative intervention with or without a shunt procedure in the case of some types of critical pulmonary valve disease or have presented impediments to the usual surgical techniques of RVOT reconstruction in some cases of TOF with coronary anomalies. Two additional clinical situations might disturb the usual preoperative planning in a patient with TOF.

Additional Congenital Cardiac Anomaly

Tetralogy of Fallot is commonly associated with other conotruncal anomalies with varying degrees of main and branch pulmonary artery stenosis or hypoplasia, coronary artery anatomical variants, aortic arch anomalies, and atrial septal defects. Right aortic arch (RAA) is found in 25% of Tetralogy of Fallot patients and, by itself, does not result in hemodynamic sequelae (Bedair and Iriart 2019). Since aberrancy of a subclavian artery with a RAA can affect arterial line placement and anomalous arches can raise airway or feeding concerns, the anesthesiologist should be aware of these otherwise benign coexisting anomalies.

Consideration of additional heart defects might alter the usual planning for TOF repair. A PDA-dependent lesion requiring ductal patency for systemic perfusion (e.g., coarctation/interrupted aortic arch) would require neonatal surgical intervention regardless of whether the specific anatomy of the TOF defect deserved immediate surgical attention. The risks and benefits of performing a palliative BTS versus complete TOF repair at the time of repairing another left heart obstructive lesion would be determined individually (Fraser et al. 2001). Most cardiac lesions with complex components of two more simple anomalies have a higher risk profile and worse short- and long-term outcome than either of the simpler

anomalies separately considered. Additionally, they are rarer; so the preoperative planning and judgments do not necessarily have the benefit of large previous experience or information in standard databases.

As previously discussed, TOF with PDA-dependent pulmonary circulation is a frequently enough seen variant of TOF that the choices and implications of surgical and palliative planning of repair are well understood. Placement of a modified or central shunt is an essential component of palliating these conditions and does not independently affect when the VSD repair and RVOT reconstruction might be done (Batra et al. 2005).

TOF in association with non-PDA-dependent anomalies such as atrioventricular canal has different considerations (Ong et al. 2012). Palliative shunting might be indicated if the clinical importance of cyanosis from the TOF component precedes the optimal time to undertake reconstruction of the endocardial cushion defect with regard to the maturity of the atrioventricular valve tissue. Whether undertaken separately or at the same time, the presence of two complex cardiac lesions usually complicates the surgical repair and adversely impacts the expected outcomes (Shuhaiber et al. 2012).

Additional Noncardiac Congenital Anomaly

TOF is frequently associated with a genetic syndrome (Gonzalez et al. 2009). In the most severe cases, consideration may be made for palliative shunting rather than complete repair if the extent or severity of the chromosome anomaly is not well defined in early infancy. Significant chromosome abnormalities are associated with a worse outcome for complete repair of TOF (Michielon et al. 2006).

Noncardiac conditions such as duodenal atresia, esophageal atresia with tracheoesophageal fistula, meningomyelocele, diaphragmatic hernia, and others may require surgical intervention in the neonate prior to when TOF might be considered for complete repair. The preanesthesia cardiac screening strategy for neonates with congenital noncardiac anomalies is not clearly defined in the literature (White 2011; Walker et al. 2009). Midline defects are associated with a higher incidence of coexisting cardiac defects, and preoperative cardiac echocardiography in addition to pulse oximetry and a chest X-ray has been advocated (Ritter et al. 1999). Recently, the recommendation to include echocardiography has been challenged as unnecessary (in the case of duodenal atresia) if the neonate's pulse oximetry, chest X-ray, and cardiac exam are unremarkable and there is no associated Down syndrome (Short et al. 2014; Nasr et al. 2010; Keckler et al. 2008).

The preanesthetic cardiac evaluation in the neonate presenting for urgent noncardiac repair should be directed at identifying lesions that might present unexpected instability under anesthesia. Although an unremarkable physical exam and pulse oximetry can be reassuring, the author opines that the most difficult anesthetic challenges could be presented by a neonate who has an undiagnosed PDA-dependent lesion that requires maintenance of the PDA for either systemic or pulmonary blood flow. Coarctation of the aorta, interrupted aortic arch, hypoplastic left heart syndrome, pulmonary atresia, and some other cardiac lesions are associated with fairly normal physical exams in the neonate when the ductus arteriosus is open. Pulse oximetry may appear unremarkable as a normal room air SaO_2 in a newborn is often no higher than 95%. In the author's opinion, identifying the presence of an occult cardiac lesion and preparing for a patient who would be critically affected by unstable ductal patency is the most important indication to proceed with cardiac echocardiography in these patients before urgent noncardiac surgery.

Physics and Physiology of Systemic Pulmonary Shunting

The use of the systemic-to-pulmonary arterial shunt has significantly advanced the palliative care of children with both single-ventricle cardiac lesions and children with two-ventricle anomalies where a temporary source of

pulmonary blood flow is required pending corrective repair. The current use of a modified Blalock-Taussig shunt (MBTS) or a Gore-Tex central shunt from the aorta to the pulmonary artery has made previous versions such as the classic Blalock-Taussig shunt and the Waterston and Potts aortopulmonary window procedures obsolete.

In the neonate, usually a 3.5 or 4.0 mm Gore-Tex tube is used to create the shunt. The physiology of blood flow from the aorta through the shunt to the pulmonary circulation follows the principles of tube physics described by Poiseuille's law:

$$\text{Flow} = \pi\left(P_1 - P_2\right)\left(\text{radius}\right)^4 / 8\left(\text{viscosity}\right)\left(\text{length}\right)$$

In this model, flow through the tube is determined by both the physical characteristics of the tube (a multiplied direct effect of the radius and an inverse effect of length), the viscosity of the blood (an inverse effect), and physiologic variables that may be controlled to some degree by manipulation of the patient's hemodynamics. The driving pressure for the shunt is the patient's blood pressure (P1), and the resisting pressure (P2) is the pulmonary arterial pressure (Fig. 17).

It is a significant advantage of the MBTS that since the patient's blood pressure even during transition is higher than the pulmonary artery pressure, the shunt is usable even before pulmonary vascular resistance has lowered to the levels seen in older infants and toddlers. Given that the expected duration of time the shunt is required is only temporary (often only 3–6 months), the fact that it will not grow with the patient is advantageous and allows the normal maturation of the pulmonary vascular bed to proceed with little chance of excessive shear stress causing damage to the pulmonary vasculature. The disadvantage of the MBTS is that it is an inefficient method of oxygenating the mixed venous blood because the gradient for oxygen uptake in the lung is narrow, and the result is that even with optimal function of the shunt, there is mild to moderate desaturation despite an elevated Qp/Qs ratio. Cardiomegaly and overcirculated lung fields on chest X-ray are common. This volume load can adversely affect the diastolic function of the ventricle, but this complication is more likely to be important in the single-ventricle model than in the two-ventricle model such as TOF.

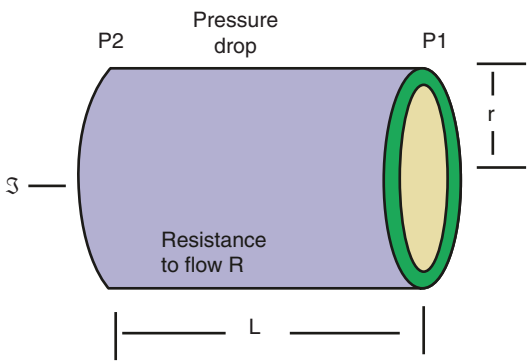

Fig. 17 Tube physics

The normal course of events in the infant who has undergone palliative shunting is that as the infant grows, the amount of pulmonary blood flow relative to the systemic cardiac output decreases, resulting in decreased saturations. Any clinical evidence of overcirculation such as failure to thrive or high-output cardiac failure resolves with growth. Chest X-ray evidence of cardiomegaly or overcirculated lung fields also resolves. In the presence of reduced pulmonary blood flow, the natural process of remodeling by regression of the medial muscular layer of the pulmonary vascular bed occurs. Although of historical interest in patients with Potts or Waterston shunts, pulmonary vascular resistance issues are not usually a feature of the TOF/MBTS patient about to have corrective surgery.

Anesthesia Issues of Systemic Pulmonary Shunting

The anesthesia management of a neonate who is undergoing placement of a palliative MBTS or central shunt is challenging. A detailed understanding of the surgical procedure and the effects of anesthetic technique, ventilation, and vasoactive medications on blood pressure (P1) and pulmonary vascular resistance (P2) is essential.

If the neonate is on a PgE infusion to maintain patency of the ductus arteriosus, arterial saturations should be in the 80s to mid-90s, depending on how effectively the pulmonary vascular resistance has fallen since delivery. In the presence of the PDA, the MBTS is often done with a median sternotomy incision so that the shunt can be completed and then the ductus arteriosus (DA) ligated through the same incision (Fig. 18). Cardiopulmonary bypass is typically available as a standby resource, but it is common to attempt to avoid it in order to avoid the hematologic intrusions on the neonate's coagulation system if possible. It is helpful to consider in siting the pulse oximeter probes, blood pressure cuff, and arterial catheter that part of the procedure will involve partial occlusion of the circulation to the right arm. Cerebral and somatic oximetries are also useful. The aorta, right innominate artery, and main and right pulmonary artery are dissected and mobilized. A small dose of heparin is administered according to institutional protocol. A side-biting C-clamp is positioned on the innominate (or subclavian) artery, and the proximal end of the 3.5–4.0 mm Gore-Tex shunt is anastomosed with a running suture. Typically, the C-clamp occludes a significant portion of the radius of the artery and causes a decrease in systemic cardiac output by causing an elevation in "mechanical resistance" analogous to increased systemic vascular resistance. In the setting of a PDA, which mimics the physiology of the pending BTS, inotropic support to maintain an adequate blood pressure may be helpful during this stage to compensate the decrease in P1 caused by the partial occlusion clamp. Changes in ventilation are not usually necessary. As this anastomosis is completed, the shunt is filled with heparinized saline, and a bulldog-type clamp is used to occlude the open end to facilitate trimming to an appropriate length for the planned distal anastomosis. The C-clamp on the innominate artery is removed and normal hemodynamics restored. Attention is then turned to the pulmonary artery, and a C-clamp is placed on the right pulmonary artery. During this time, pulmonary blood flow will be diminished by nearly half, and as the PDA is providing blood flow from the distal transverse aorta to the left pulmonary artery, inotropic support of blood pressure (P1) will continue to be useful. Additional adjustments in FiO_2 and minute ventilation in order to maintain arterial saturations in the 80s are often required. In theory, pulmonary artery hypertension should be avoided as an elevated P2 could compromise blood flow via the DA; however, the deleterious effects of hypocarbia on cerebral blood flow should also be considered in the neonate. The minimal benefit of lowering PVR with hyperventilation should be weighed against the intrusion on neonatal cerebral autoregulation associated with acute hypocarbia. When the shunt is complete, the C-clamp on the pulmonary artery and the occlusion clamp on the shunt are removed as the distal anastomosis is deaired and the suture tightened. Since there is now pulmonary blood flow via the DA and the shunt, the SaO_2 normally rises to or above the mid-90s. The FiO_2 should be decreased to 30–40% during this time. The expected SaO_2 in a term size neonate with a 3.5–4.0 shunt should be 80–90%. Attention is turned to the PDA, and after test occlusion with a clamp to verify the function of the MBTS is adequate to oxygenate the patient at 30–40% FiO_2, the DA is ligated.

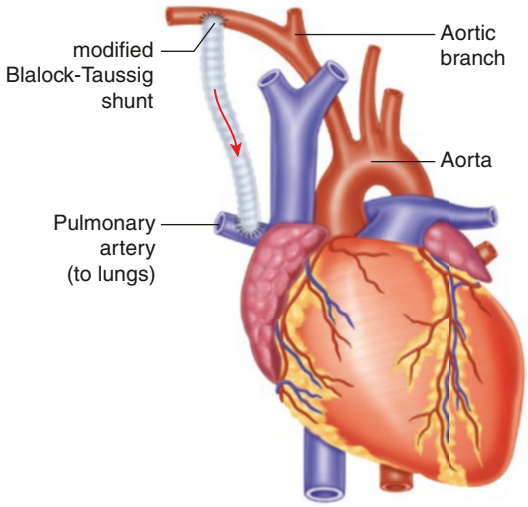

Fig. 18 BTS creation

In the hemodynamic model of an unrepaired TOF patient without a PDA, the urgent or emergent placement of a MBTS is a more difficult exercise in hemodynamic manipulation. The order of the surgical procedure is as described

above, but there is no safety margin of a DA supplying a cardiac output-dependent source of pulmonary blood flow during the procedure. Antegrade pulmonary blood flow relies on adequate RV filling, an adequately maintained systemic vascular resistance, and control of heart rate and contractile function to avoid a hyperdynamic cardiac state. Failure to accomplish these hemodynamic goals is associated with progressive and paroxysmal hypercyanosis. During creation of the MBTS, placement of the C-clamp on the innominate or carotid artery is usually well tolerated initially as it creates mechanical resistance to systemic cardiac output that reduces right-to-left shunting across the VSD similar to the administration of an alpha-adrenergic agent. In general, inotropic support during placement of the proximal end of the shunt is not required and may precipitate hypercyanosis by causing a hyperdynamic infundibulum to become more obstructive to RV blood flow into the pulmonary artery. In the absence of a PDA, when the pulmonary artery is partially occluded to complete the distal anastomosis of the shunt, SaO_2 decreases markedly. Manipulations of ventilation and FiO_2 are often only minimally successful. Attempts to augment cardiac output are counterproductive as the right-to-left shunt is worsened. Adequate volume loading and careful control of heart rate are the only manipulations available to the anesthesiologist. Careful communication between the surgeon and anesthesiologist is required when the patient experiences significant arterial desaturation to consider whether the patient is too unstable to complete the shunt without instituting cardiopulmonary bypass.

Troubleshooting the apparently failing shunt in the operating room is an exercise of collaboration and communication between the surgeon and anesthesiologist. After the shunt is completed, regardless of whether CPB was utilized, the physiologic model of TOF converts to the model described by the components of Poiseuille's law with P1 and P2 controllable by the anesthesiologist. Inotropic support to increase shunt flow is common for a short time after surgery when the patient is at risk of shunt thrombosis. The critical clinical dilemma in the operating room or the post-op intensive care unit is when the patient's saturations decline despite adequate hemodynamics. In the operating room, it is easy for the surgeon to palpate the shunt or verify flow by using a handheld Doppler. If the shunt is patent, decreased shunt flow is usually related to decreased P1 or blood pressure. To a lesser degree, elevations in P2 or pulmonary vascular pressures may also decrease shunt flow. The range of clinically observed variation of PVR is narrow compared to the absolute levels of SVR, and in the absence of hypotension, P2 issues are not as often associated with shunt malfunction. Appropriate management of cardiac output and pulmonary vascular resistance should result in predictably stable arterial saturations. If this cannot be accomplished in the operating room, it is necessary to verify that there is not a technical problem with the shunt causing decreased flow. It may be useful to connect a needle and pressure tubing to a transducer and directly measure the pulmonary artery pressure distal to the shunt. If it is low, shunt failure is the diagnosis and is due to a technical issue with one of the anastomoses, thrombosis, or both. If the pressure is high, the patient has pulmonary hypertension, and therapy with inhaled nitric oxide is indicated (Bushman 2001). Nitric oxide is preferred in this situation to systemic vasodilators or milrinone because systemic vasodilation that would lower P1 is avoided.

In the intensive care unit, troubleshooting an apparently failing shunt is more problematic because the sternotomy incision is usually closed. Optimization of hemodynamics and pulmonary resistance is accomplished. A decrease in the intensity or the absence of an audible shunt murmur is suggestive of shunt failure, and echocardiography should be utilized to visualize the shunt. If patency of the shunt is in question or the patient clinically exhibits minimal signs of pulmonary blood flow with decompensation, shunt thrombosis should be suspected and cardiothoracic surgical and anesthesiology teams should be mobilized while intravenous heparin and fluid boluses are administered in an attempt at thrombolysis. If despite echo evidence of shunt

patency and an adequate cardiac output, arterial saturations are still inadequate, a trial of nitric oxide for presumed pulmonary hypertension is indicated. If the patient continues to be desaturated, evaluation in the cardiac catheterization suite may also be needed to assess the patency of the shunt.

Anesthesia Issues of the Patient with a BTS for Complete Repair

After successful palliation with a MBTS, the TOF patient will present later for corrective repair as decreased saturations and hypercyanotic spells are mitigated by the shunt. The anesthetic considerations are primarily directed at maintaining the relationship between P1 and P2 without regard for intracardiac right-to-left shunting as determined by the dynamic determinants of infundibular obstruction. A TOF patient with a patent shunt cannot have a "Tet spell" provided blood pressure and cardiac output are maintained during the induction and maintenance of anesthesia. If a patient with a shunt is having hypercyanosis, the patency of the shunt should be considered suspect. Management is then directed at optimizing preload and afterload and controlling contractile state and heart rate in determining the patient's right-to-left shunting across the VSD and the resulting arterial saturation.

As with any patient with a PDA, a patient with a MBTS who is placed on cardiopulmonary bypass (CPB) has obligatory runoff through the shunt that decreases systemic perfusion from the aortic cannula. This is associated with decreased venous saturations on bypass that seem unrelated to the flow rates calculated for the patient's size. The initial maneuver performed by the surgeon after CPB is initiated is to ligate the shunt. Communication with the perfusionist regarding the presence of the shunt and when it is ligated is useful in interpreting the adequacy of calculated flows on CPB and the significance of mixed venous saturation monitoring from the venous circuit.

Conclusion

In approximately 80 years, TOF has benefited from an evolution of palliative and corrective procedures that optimized the natural history of patients with the disease. It is currently accepted that patients with TOF not only have a limited duration of hypoxemia as infants but also undergo surgical repair with an acceptably low mortality rate and excellent short- and midterm outcome. The late outcomes are also excellent, even though for some patients there is procedural reintervention for issues related to the RVOT. The complications of pulmonary vascular disease, left ventricular dysfunction, and arrhythmias are now largely of historical interest. Reoperation to revise the RVOT and implant a pulmonary valve is of low risk and predictably good outcome. The functional status and life expectancy of most adult patients with TOF are normal or nearly normal.

TOF also serves the practitioner with an excellent model to consider the unique correlation of anatomy and physiology in unrepaired TOF as well as the considerations of the arterial shunt model in the two-ventricle cardiac lesion.

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Transposition of the Great Arteries

Clementine H. Vo and Gerald A. Bushman

Abstract

A 6-h-old male infant was delivered with Apgar scores of 6 and 4 at a community hospital. Initial arterial oxygen saturation (SaO_2) was 78% and it has decreased to 56% despite endotracheal intubation and supplemental oxygen. The blood pressure is 40/22 with a heart rate of 188. There is a significant metabolic acidosis on an arterial blood gas.

Keywords

Tricuspid valve · Pulmonary vascular resistance · Left ventricular outflow tract Pulmonary blood flow · Right ventricular outflow tract

Case Presentation

A 6-h-old male infant was delivered with Apgar scores of 6 and 4 at a community hospital. Initial arterial oxygen saturation (SaO_2) was 78% and it has decreased to 56% despite endotracheal intubation and supplemental oxygen. The blood pressure is 40/22 with a heart rate of 188. There is a significant metabolic acidosis on an arterial blood gas.

- What intervention should be done immediately? How is a fetal pattern of circulation restored in the neonate and of what value is it when the diagnosis of distress is undetermined?
- After an echocardiogram reveals transposition of the great arteries (TGA) with an intact ventricular septum and a restrictive atrial septal defect (ASD), plans are made to perform an atrial septostomy at the bedside. Why is a septostomy required if the ductus arteriosus is open with prostaglandin E (PgE)?
- How can the adequacy of resuscitation be assessed after septostomy?
- When should corrective surgery be performed?
- While discontinuing cardiopulmonary bypass after arterial switch, the patient is hypotensive despite elevated central venous pressure (CVP). How should this be assessed? What is the differential diagnosis?
- One week after arterial switch procedure, the patient is feeding poorly and is scheduled for a gastrostomy tube. What considerations are important in planning anesthesia care?

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Embryology

TGA represents about 5% of all patients with congenital heart disease and approximately one-third of conotruncal defects with situs solitus (Ferencz et al. 1995) (Fig. 1). TGA does not represent an alternative model of fetal or neonatal blood flow with a clear morphogenic explanation, and early attempts to understand the anatomy and postulate the embryology relied on surveys of autopsy specimens. Because the lesion is lethal during early infancy, an abundance of cadaver material has been available through the years showing many variations and subtle anatomic nuances that are difficult to classify in a unifying embryologic theory (Samànek 2000).

Two main hypotheses are recognized (Marino et al. 2002). Gore and Edwards proposed that TGA was caused by the lack of the normal clockwise rotation of the aorta (AO) toward the left ventricle (LV), presumably due to the lack of maturation of the subpulmonary conus with persistence of the subaortic conus (Goor and Edwards 1973). ("Conus" specifically refers to the muscular cardiac segment between the atrioventricular valves and the semilunar valves as defined by Drs. Van Praagh and Van Praagh.) In this scenario, TGA is an extreme case of aortic malposition that is on the spectrum of defects that includes malalignment ventricular septal defects (VSDs), tetralogy of Fallot, and double outlet right ventricle. This theory seems to adequately explain the morphologic differences seen in TGA related to variations of the right ventricular outflow tract (RVOT) or left ventricular outflow tract (LVOT) and the positions of the pulmonary artery and VSD, but the presentation of TGA with an intact ventricular septum is difficult to explain. A simpler theory by de la Cruz offers that linear rather than spiral septation of the truncus occurs and the failure of the aortopulmonary septum to spiral leads the aorta to remain in continuity with the anterior conus of the right ventricle (De La Cruz and Da Rocha 1956). This explanation, however, fails to clarify the origin of the large variability of conal anatomy that presents in TGA.

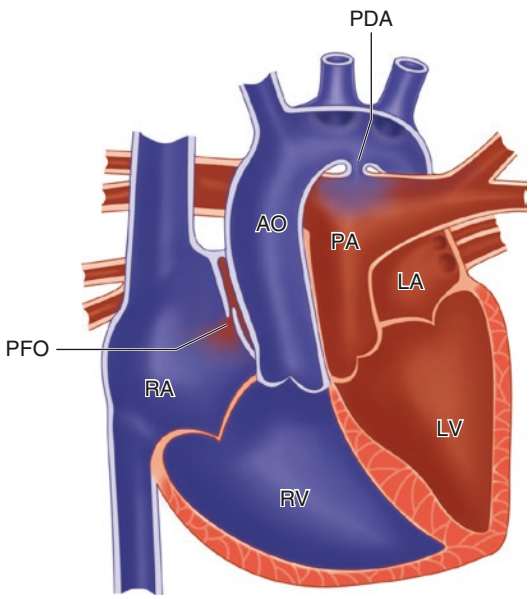


Fig. 1 Transposition of the great arteries

Terminology and Anatomy

Historically, the basis for terminology describing a complex cardiac defect is derived from pathologic examinations of cardiac specimens and refined by clinical and physiologic correlation and ultimately an understanding and description of the failure of morphologic development. The absence of a unifying theory of the maldevelopment of the heart in TGA and the large variability of anatomic presentations related to the position of the great vessels relative to each other and observed outflow tract abnormalities have made consistent descriptive terminology problematic (Mair et al. 1971). A nomenclature report on TGA published in a review in 2000 provides details of widely accepted terminology that are beyond the scope of this chapter (Jaggers et al. 2000).

The classification suggested by Van Praagh describes morphology and forms the general basis for most imaging descriptions of the anatomic variables in TGA (Houyel et al. 1995; Van Praagh 1984; Van Praagh et al. 1975). This format is useful for conceptualizing the malformation and its variations. Cardiac position is left sided (levocardia), right sided (dextrocardia), or midline (mesocardia). The main cardiac segments are the atria, ventricles, and

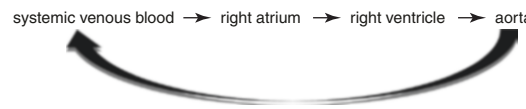
great arteries. The connecting cardiac segments are the atrioventricular (AV) canal complex between the atria and ventricles and the conus between the ventricles and the great arteries. Malpositions of the main segments may be described as solitus, inversus, or ambiguous. Additionally the visceral situs is described as situs solitus if the pulmonary (right) atrium is on the right and the right-sided abdominal organs (the liver, gall bladder) and the trilobe lung are also on the right and the pulmonary venous (left) atrium and the left-sided abdominal organs (the stomach, spleen) and the bi-lobe lung are on the left. Situs inversus is mirror image reversal of the normal situs solitus. Situs inversus is rare and not usually associated with medical issues. Diagnosis is usually incidental, while the patient is undergoing imaging for other conditions. Situs ambiguous refers to the random abnormal distribution of the abdominal organs and is highly associated with heterotaxy cardiac malformations, including single ventricle lesions.

The sequential segmental analysis usually reported by echocardiogram in TGA includes the cardiac position and direction of the apex, the position and morphology of the atria, the atrioventricular connections, the ventriculoarterial (VA) connections, and the positions of the great vessels. Atrioventricular connections are concordant when the systemic venous right atrium (RA) empties into the morphologic right ventricle and the pulmonary venous left atrium empties into the morphologic left ventricle. Discordance refers to when the systemic venous right atrium empties into the morphologic left ventricle and the pulmonary venous left atrium empties into the morphologic right ventricle. The discrete commitment of the atrioventricular apparatus to the ventricular inlet is also described. A double inlet ventricle has both AV valve apparatus committed to the ventricular inlet. Ventriculoarterial or outlet connections are referred to as concordant if the pulmonary artery is connected to the right ventricle and the aorta to the left ventricle and discordant if the pulmonary artery is connected to the left ventricle and the aorta to the right ventricle. Double outlet connections refer to one great vessel and more than 50% of the other committed to either the right or the left ventricle. Note that the above classification describes the intrinsic connections of the main cardiac and connecting segments sequentially and does not describe the positions of the great arteries relative to each other.

Simple Transposition of the Great Arteries

Pathologic heart specimens showing an aorta arising from the right ventricle and the pulmonary artery from the left ventricle have been observed since the late 1700s (Leibman et al. 1969). Historically, more than half of infants presenting as neonates with severe cyanosis have the diagnosis of TGA (Farre 1814). TGA is associated with an intact ventricular septum 55% of the time and with a VSD of variable size 45% of the time. The age of the demise of such patients historically seemed related to the size of the atrial septal defect, with most not surviving infancy (Leibman et al. 1969). Contemporary analysis shows that TGA occurs approximately 1:3200 live births with a strong male predilection of 1.6–3.2:1 (Hoffman and Kaplan 2002). The segmental description of simple TGA is atrioventricular concordance with ventriculoarterial discordance (Van Praagh 1984; Allen et al. 2001a). The designation of the spatial relationship of the great vessels as "*D*" or "*L*" completes the anatomic description. It is important to note while the terms "TGA" and "d-TGA" are commonly used synonymously, the reader understands that d-TGA specifically refers to an anterior and rightward aorta. D-TGA refers to the location of the right and left ventricles in their normal positions. The aorta is usually anterior and to the right of the pulmonary artery (D), although occasionally it may be directly anterior or anterior and to the left (L).

The hemodynamic derangement from TGA is derived from the two parallel loops of circulation created by the transposed great arteries (Ewer et al. 2012). One loop is:



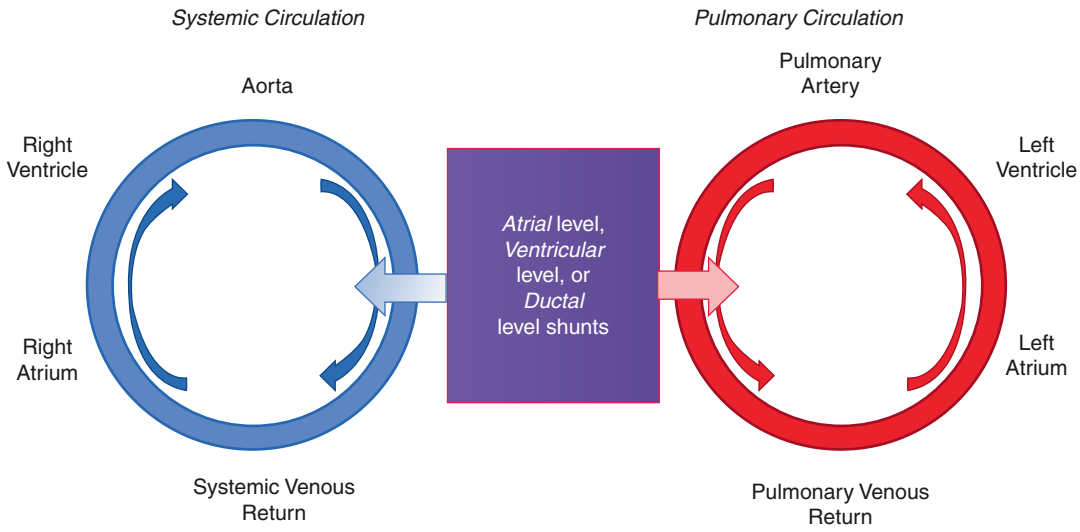
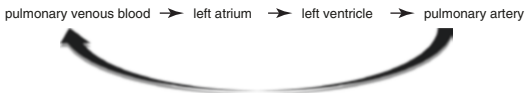


Fig. 2 Arterial and venous mixing in TGA

Likewise, the other loop is:



In the worst case, the highly oxygenated blood in the pulmonary venous loop never accesses the systemic circulation, and the systemic output from the aorta in the systemic venous loop never accesses the pulmonary vascular bed to allow oxygenation and carbon dioxide exchange. Extrauterine survival requires a site of mixing such as an intracardiac shunt (ASD or VSD) or extracardiac shunt (patent ductus arteriosus [PDA]) (Fig. 2).

An additional hemodynamic issue important in the first few months of life is related to the pulmonary vascular bed being in connection with the left ventricle. In utero and during transition from fetal to neonatal circulation, the pulmonary vascular resistance (PVR) is high. At birth, the PVR decreases rapidly as the lungs are expanded and the vascular bed relaxes because of the effect of vasoactive mediators and oxygen (Fig. 3). In the weeks and months following birth under normal circumstances, the medial muscle layer of the pulmonary arteriole regresses and remodels. In this period the left ventricle will decondition as PVR decreases, unless there is a nonrestrictive VSD to allow the resistance circuit of the LV to include systemic circulation via the RV. The process of LV deconditioning usually begins around 21 days of life (Rito et al. 2022).

Although recent recommendations show screening of newborns routinely with pulse oximetry is effective in detecting cyanotic lesions such as TGA, this practice only benefits patients with TGA who have an adequate ASD to survive the early neonatal period (Ewer et al. 2011; Rasiah et al. 2006). Unfortunately, a routine obstetrical ultrasound may not carefully evaluate the outflow tracts and great vessels in the fetus, but a carefully performed fetal cardiac ultrasound that identifies TGA potentially allows the fetus to be delivered in a facility prepared for the expectant use of prostaglandin E (PgE) and transport availability for subspecialty cardiology care (Calderon et al. 2012). Prenatal diagnosis reduces the potential neurodevelopmental complications that may arise in a neonate with TGA when compared to patients whose diagnosis is delayed until severe cyanosis and cardiovascular collapse occur after birth because the patent foramen ovale is too small for adequate mixing and the ductus arteriosus closes (Blalock 1950). Without intervention, TGA without a sufficient intracardiac or extracardiac shunt is universally fatal.

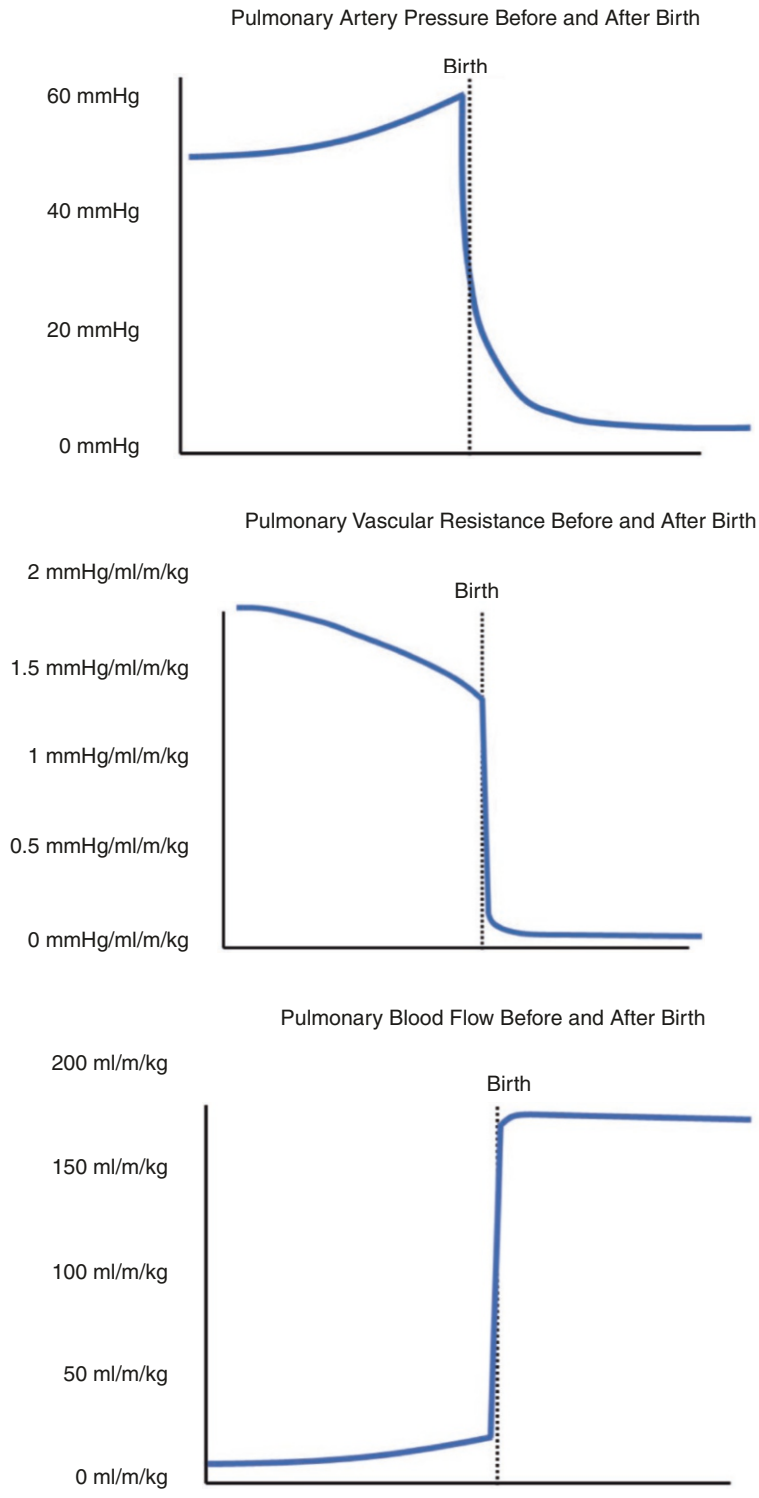


Fig. 3 PVR transition

Clinical Presentation

The clinical presentation of neonates with TGA is variable. For survival there must be a shunt at the atrial level, the ventricular level, or a patent ductus arteriosus. If there is inadequate shunting, cyanosis is severe and cardiovascular collapse occurs rapidly. Although most neonatologists would institute PgE in the face of cyanosis without overt respiratory distress syndrome, a PDA is not as efficient as an atrial septal defect in providing mixing of systemic venous and pulmonary venous blood. For this reason, after diagnosis by echocardiogram, emergency balloon septostomy is routinely performed either at the bedside with echocardiographic guidance, or in the catheterization lab if the septostomy is anticipated to be complex. The helpfulness of a ventricular septal defect, if present, is variable. Depending on the size of the VSD and in particular the morphology of the conal septum, the VSD may be either an effective source of mixing or ineffective because the streaming characteristics of blood ejected through the conal septum render the VSD inoperative as a site of mixing.

Patients with TGA who have large ASDs or VSDs may be more difficult to detect at birth. Their cyanosis may be mild to moderate and if overlooked, the other physical signs of TGA may not be impressive. As the PVR decreases in the days and weeks after birth, a normal infant demonstrates a modest increase in arterial saturation, but the infant with TGA will demonstrate progressive high-output heart failure and continued desaturation. Chest X-ray will show increased pulmonary vascular markings consistent with pulmonary overcirculation and cardiomegaly, especially if there is an unrestrictive VSD present. Symptoms and signs of a left-to-right shunt such as poor weight gain, diaphoresis, tachycardia, and a cardiac gallop may be present. Persistent cyanosis is a function of the intracardiac mixing that occurs despite an elevated Qp/Qs ratio. The term "reverse differential cyanosis" is often used to describe cyanosis that occurs in the upper extremities more than in the lower extremities. This occurs in the patient with TGA with pulmonary hypertension or coarctation. In "differential cyanosis," there is more cyanosis in the lower extremities than the upper extremities, such as in the newborn with normally related great arteries.

Historical Therapeutic Approaches and Outcomes

Before discussing the details of contemporary surgical management of TGA, it is useful to review the advances in surgical technique and physiologic insight that led to the current application of the arterial switch. Early attempts to palliate TGA preceded the era of open-heart surgery. Autopsy specimens had led to the understanding that the age of a patient's demise was strongly related to the presence and size of an intra-atrial communication. The Blalock-Hanlon procedure was described in 1950 and represented the first palliative operation that seemed to be associated with improved survival in older infants compared to the natural history of the unrepaired lesion (Blalock 1950; Blalock and Hanlon 1948). Using a modified technique of inflow occlusion, a surgical ASD was created via a right thoracotomy. Increasingly surgery was performed in younger infants with an expected early survival over 85%, with most patients operated on from the 1940s to the 1970s experiencing improvements in percent arterial saturation (Hermann et al. 1975). The midterm and late results were not nearly as good (Alexi-Meskishvili and Sharykin 1984). Mortality in the weeks after surgery was still substantial, but survivors of the first few months tended to have prolonged survival to 10 years or more. Nonetheless, it was clear that a more definitive approach to palliation was required.

Early attempts to repair the lesion by arterial switch were largely unsuccessful because of the technical difficulty in transferring the coronary arteries to the neoaorta (Yacoub and Radley-Smith 1978; Senning 1959; Bailey et al. 1954). Animal experiments by Alfred Blalock and C. Rollins demonstrated in a canine model the feasibility of connecting the pulmonary veins to the superior vena cava (SVC) and the right atrium

(RA) and hypothesized that a similar approach might be made in infant patients with TGA (Blalock and Hanlon 1948). This introduced consideration that instead of reversing the aorta and pulmonary artery, the pulmonary and systemic venous pathways might be reconstructed, obviating the need for coronary reconstruction inherent to the arterial switch. In 1952, Walton Lillehei attempted an extracardiac "venous switch" by connecting the right pulmonary veins to the right atrium and the inferior vena cava (IVA) to the left atrium (Lillehei and Varco 1953). Further modifications by Thomas Baffes and Willis Potts in 1956 were described and as these procedures were done without cardiopulmonary bypass, they were commonly used for the next 10 years with increasing short-term success (Baffes 1956). In 1954 Harold Albert published the use of an intra-atrial flap to redirect systemic and pulmonary venous flow to the contralateral atrioventricular valve in dogs (Albert 1954). William Mustard and others advanced the technique that became the Mustard procedure, which used a prosthetic patch to create the intra-atrial baffle on cardiopulmonary bypass, diverting pulmonary venous blood to the tricuspid valve and systemic venous blood (SVB) to the mitral valve (Mustard et al. 1964). Also in the late 1950s, Ake Senning demonstrated the atrial switch could be done with autologous material (pericardium), although the procedure seemed more difficult (Senning 1959) (Fig. 4). Initially in the 1960s Senning's procedure was largely abandoned in small infants because the technical challenges of creating the patch reduced the size of the atrial chambers, and low cardiac output after surgery was common (Mustard et al. 1964). The Mustard procedure was more successful in most surgeons' hands and its survival statistics continued to improve. However by 1975, the midterm shortcomings of the Mustard procedure were becoming more obvious as older survivors presented with right- and left-sided venous obstruction as they grew (Quaegebeur et al. 1977). Arrhythmias and heart block were also increasingly common by 10 years after a Mustard procedure. Resurgent interest in Senning's procedure, which avoids nonautologous materials, and the increasingly

Systemic venous blood is baffled (SVB) through the ASD to the mitral orifice, enters the LV and is ejected out the MPA.
Pulmonary venous (PV) blood is baffled through the ASD to the tricuspid valve, enters the RV and is ejected out the aorta.

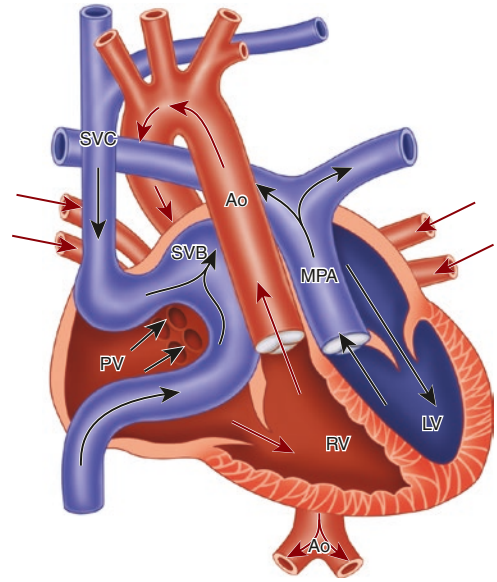


Fig. 4 Mustard/Senning intracardiac blood flow

successful technical application of the technique in small infants, made it the most common palliative procedure performed for TGA through the 1980s (Senning 1959). Baffle obstruction due to patient growth in the first 10 years was reduced compared to the Mustard procedure and cardiac surgeons better managed the technical complexities of the baffle in infants. In many centers, infant survival of the Senning and Mustard procedures was equivalent and the midrange outlook for the patients with Senning baffles somewhat better (Williams et al. 2003). With increasing survival of TGA patients, anesthesiologists may see an increase in older patients presenting with baffle obstruction or stenosis; these patients can present with SVC (more commonly) or IVC syndrome, hepatomegaly, or if on the pulmonary venous side, florid pulmonary edema.

In institutions performing Senning and Mustard procedures for TGA, care of the neonate and young infant was focused on expedient cardiac diagnosis and resuscitation of hypoxemia and low cardiac output. Atrial septostomy during

stabilization was essential and was performed by balloon or blade, usually in the catheterization laboratory. As adequate atrial mixing was established, vasopressor and PgE infusions could usually be weaned and discontinued. Oxygen and ventilator therapy were also weaned and discontinued. In many instances, the stabilized infant was observed to make sure that atrial mixing remained adequate and that pulmonary vascular resistance was falling and then discharged home with careful follow-up.

In the 1980s the mortality for complex cardiac surgery in neonates was higher than contemporary survival data, partly because other than extracorporeal membrane oxygenation, reliably effective medical therapy for pulmonary hypertension was not available. (Nitric oxide by inhalation became available in the early 1990s in some institutions, and in that decade the management of persistent pulmonary hypertension in pediatric cardiac patients who were still in transition when undergoing surgery became more effective.) It was common to defer when possible repair of TGA for at least a few weeks to months. When the infant was observed to have overcirculation of the lungs and mild high-output heart failure, an atrial switch procedure was performed electively. Most institutions felt that the intra-atrial baffle part of the procedure was technically easier on an infant who was 4 kg rather than on a neonate, and surgery better tolerated when PVR had fallen. With regard to intraoperative management of inspired oxygen (FiO_2), minute ventilation, and expected arterial saturations (SaO_2), cardiac anesthesiologists in that era learned from the neonatal care of infants with TGA that although increases in pulmonary to systemic flow ratios (Qp/Qs) could be accomplished with ventilator maneuvers and increased FiO_2, in the presence of adequate atrial level mixing, the changes in Qp/Qs are not reflected in major improvements in arterial saturation.

As survival data from patients with TGA from the 1950s onward accumulated, it became obvious that although atrial switch palliation was superior to atrial septectomy in improving survival through infancy and childhood, there were still long-term challenges for the 84% who survived 10 years and the 77–80% who survived 20–30 years (Williams et al. 2003). Event-free incidence in survivors over three decades was less than 20% (Cuypers et al. 2014). Events were described as late failures of the operative procedure (reoperation required for baffle-related obstruction of systemic or pulmonary venous flow). Events could also be natural history issues such as arrhythmias and heart block, and late heart failure due to systolic dysfunction and tricuspid regurgitation as the inability of the right ventricle and tricuspid valve (physiologic "mitral valve") to function as systemic pumping structures over a lifetime became more obvious (el-Said et al. 1972; Culbert et al. 2003; Martin et al. 1990).

Contemporary Management and Interventions Prior to Surgery

Medical stabilization of the newborn diagnosed with TGA involves managing acidosis and hypoxemia that occurs when the intracardiac shunts are insufficient to allow adequate mixing and the ductus arteriosus closes. In any newborn patient with cyanosis of cardiac origin, PgE is administered to reconstitute ductal patency and allows blood flow into the lungs from the aorta (Fig. 5). Although in TGA, this maneuver increases pulmonary blood flow, unless there is an adequate amount of intracardiac mixing, the improvement in cyanosis may be negligible. Therefore, in the absence of a large ASD or VSD, balloon or blade atrial septostomy is usually required to improve atrial level mixing (Fig. 6). Successful enlargement of the atrial level shunt should result in immediate improvement in arterial saturation (SaO_2) as measured by pulse oximetry.

Some neonates and infants who have adequate mixing after an atrial septostomy may fail to improve their oxygen saturations if they also have pulmonary hypertension (Newfeld et al. 1974). Pulmonary hypertension as a transitional problem in neonates with cardiac disease is common, usually transient, and may be managed with nitric oxide by inhalation. Additionally, TGA

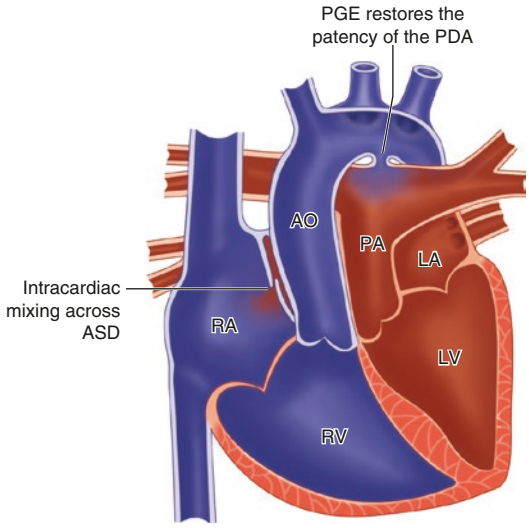


Fig. 5 TGA/PDA

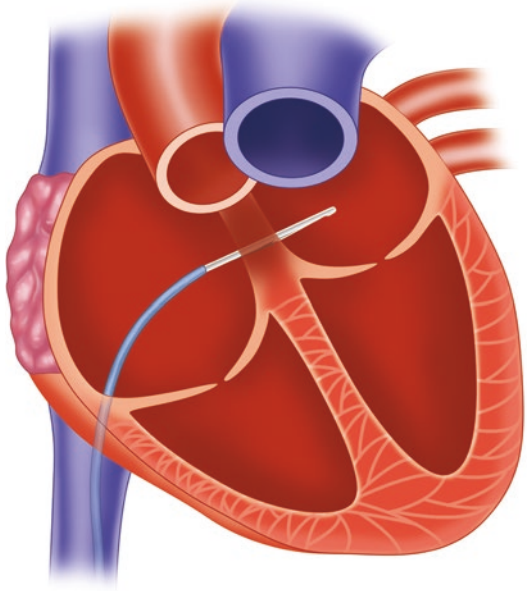


Fig. 6 Atrial septostomy

patients are known to occasionally present with persistent pulmonary vascular disease that seems out of proportion to the duration of time they experience physiology that predisposes them to pulmonary overcirculation (Roofthooft et al. 2007). In this small subset of TGA patients, pulmonary hypertension may be less reactive, and careful hemodynamic assessment is required before surgical correction is undertaken to rule out other lesions that may have put the pulmonary vascular bed at risk by elevating pulmonary venous pressure.

An unresolved issue is the contribution of atrial septostomy to brain injury due to embolic stroke or intracerebral hemorrhage. Although the Rashkind procedure has been performed since the 1960s, the issue of optimizing neurodevelopmental outcome was less relevant in the era where surgical outcomes were not as successful (Rashkind and Miller 1966). As surgical palliation with the Senning and Mustard procedures was replaced in most centers with surgical correction by the arterial switch, survival outcomes continued to improve through the 1990s until today. Much research is now devoted to optimizing functional outcomes, including neurodevelopmental achievement and long-term freedom from reoperation. When imaged with MRI, patients with TGA (like many cardiac anomalies), have a higher incidence of structural brain anomalies and periventricular leukomalacia than infants without cardiac defects. Although there is literature indicting the septostomy procedure as an additional risk for brain injury by provoking embolic phenomena, the clinical context of hypoxia and decreased cardiac output may play a contributory role (McQuillen et al. 2006; Petit et al. 2009). The independent relation of the septostomy in causing neurologic injury has been both confirmed and discarded by conflicting studies.

The presence of a VSD is an unreliable site of mixing in many cases because of streaming of pulmonary and systemic venous blood past the septal defect into the respective great vessels. Nonetheless, a VSD does have implications on the hemodynamic modeling of left ventricular systolic performance prior to surgery in that if the VSD is large enough, the LV does not decondition as the PVR drops. Those with a large, unrestrictive VSD can have LV pressures that are near-systemic (Latham et al. 2015). In TGA with an intact ventricular septum, the normal fall in pulmonary vascular resistance that occurs the first few weeks of life is associated with reduced systolic pressure in the left ventricle. In

the era of atrial switch palliation where the left ventricle remained the pulmonary ventricle, this was not a relevant issue. But the current application of the arterial switch procedure that restores the left ventricle as the systemic ventricle makes it an important consideration (Adhyapak et al. 2007). The arterial switch procedure is usually performed the first few weeks of life in order to avoid imposing systemic workload on a deconditioned left ventricle. Performing the procedure while the LV is still conditioned to perform at "systemic" pressures is associated with improved outcomes and reduced need for prolonged vasopressor support or extracorporeal support for ventricular failure.

Contemporary Surgical Management and Outcomes

In the 1970s when most infants were undergoing Mustard and Senning procedures for TGA, it was identified that patients with TGA/VSD continued to have poor outcomes despite early good results in TGA with intact ventricular septum. The arterial switch procedure was therefore applied to these patients with poor but improving short-term outcomes. Unlike the Norwood procedure for hypoplastic left heart syndrome where the "transfer of technology" was very slow and widespread improvement in outcomes delayed, the technical details associated with success of the arterial switch were widely adopted, and by the mid-1980s most neonates with TGA with or without a VSD underwent arterial switch, accomplishing anatomic correction.

The arterial switch operation (ASO) was described by Jatene in 1976 and has undergone modifications, including those proposed by Lecompte in order to improve the technical performance of the great vessel reconstruction, and improvements in techniques of coronary reimplantation especially when there are variations from the normal origination of the coronary ostia. Although there are institutional variations in technique, the common elements are:

1. Median sternotomy is performed with harvesting of pericardium for patch augmentation of the neopulmonary artery or septal defect closure.
2. The coronary artery anatomy is inspected to identify coronary anomalies and plan reimplantation sites.
3. The great vessels, branch pulmonary arteries, and patent ductus arteriosus are mobilized.
4. Heparin is administered and cardiopulmonary bypass initiated with bicaval or single atrial venous cannulation. The PDA is ligated as bypass is initiated. Temperature and perfusion techniques vary among institutions, but deep hypothermic circulatory arrest is rarely indicated.
5. Venting of the left ventricle is accomplished by a pulmonary venous catheter or through the ASD.
6. Aortic occlusion and cardioplegia administration are routine.
7. Patch closure of any septal defects is done.
8. The aorta is transected above the sinotubular junction and the coronary arteries are disconnected with a button of aortic tissue.
9. The main pulmonary artery (MPA) is transected.
10. Coronary button reimplantation to the neoaorta and anastomosis of the ascending aorta to the proximal neoaorta is performed.
11. Relocation of the pulmonary artery bifurcation to the neopulmonary artery with patch augmentation as needed is done.
12. Ultrafiltration is commonly utilized (Fig. 7)

De-airing of the heart and reperfusion after removal of the aortic cross clamp begins the period where the reconstruction is critically assessed. Coronary perfusion should be immediately obvious and myocardial recovery rapid as evidenced by the return of a normal electrocardiogram. During reperfusion, echocardiographic evidence of adequate systolic ventricular function should be verified with particular assessment for wall motion abnormalities of the left ventricle that might indi-

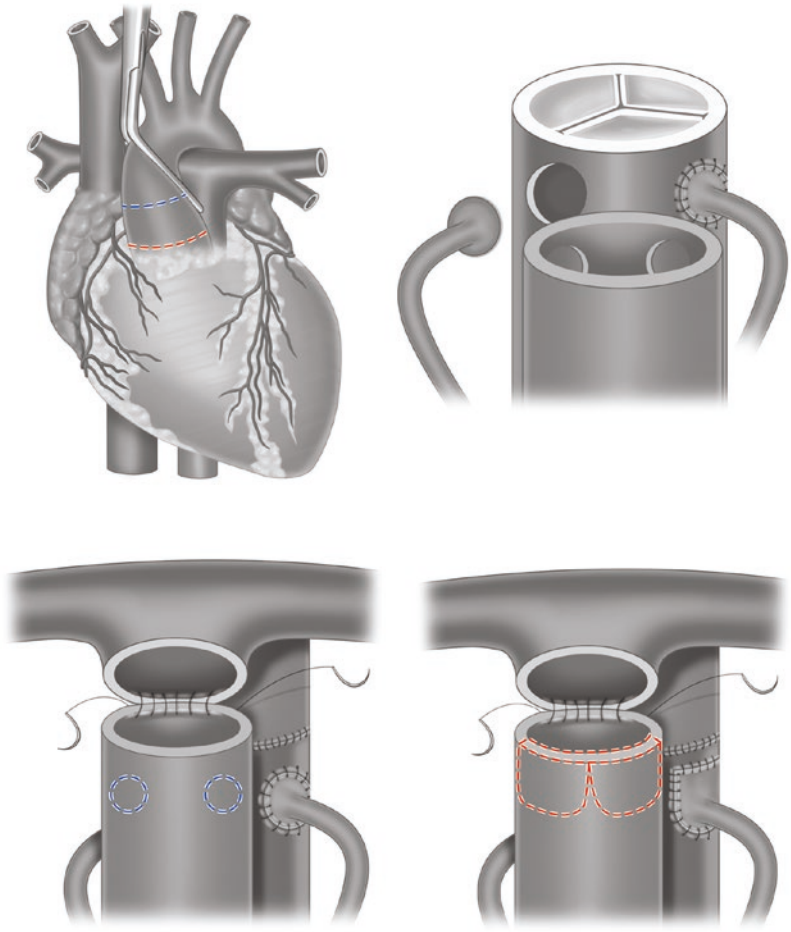


Fig. 7 Arterial switch

cate a technical problem with coronary reimplantation. Usually coronary issues result in overt ventricular dysfunction in the distribution of the left main or right coronary artery, and this assessment is straightforward when the aortic occlusion time is not excessive and myocardial protection meticulously performed. However, in the event of a prolonged cross-clamp time or technical issues that interfere with adequate cardioplegia administration, the differential diagnosis of ventricular systolic dysfunction is more problematic (coronary issue versus myocardial stunning). Residual air in the coronaries can lead to frank myocardial ischemia; in the setting of an already compromised coronary artery (e.g., kinking or stretching after reimplantation), ischemia-induced dysrhythmias are not uncommon. Direct inspection of the coronary arteries and their perfusion as well as the epicardial appearance of well-perfused myocardium is essential.

The issue of LV reconditioning after repair in the TGA patient manifests even after successful surgery. (The fragility under stress of apparently "normal" ventricular function may be especially important in infants whose convalescence after surgery is complex, necessitating additional operative procedures or imaging studies requiring anesthetics.) The only patients who (intraoperatively) retain systolic LV performance adequate to easily assume systemic workload are the TGA patients who have a large VSD. All others can be assumed to have some intolerance to

the requirement that they accomplish a "normal" systolic pressure after repair. This may persist for days to weeks after repair.

Additionally the issue of poor ventricular diastolic function makes intraoperative management of the patient's hemodynamics challenging. The conduct of reperfusion after removal of the aortic cross clamp is critical. The LV after arterial switch is extremely noncompliant and easily distends with small volume overload. The release of the vena cava tapes and filling of the heart on bypass require great care and are just as critical as when weaning from bypass in order to avoid distending the LV. Ventricular distension causes longitudinal stretch of the coronary arteries leading to further ventricular dysfunction due to myocardial ischemia. The author's preference is preemptive inotropic support with dopamine and low-dose epinephrine, in addition to lusitropic support with milrinone, in order to optimize systolic and diastolic function with a small left ventricular end-diastolic volume. The value of nitroglycerin to prevent coronary spasm in neonates is controversial. Potent vasodilators such as nitroprusside are difficult to use in neonates with poor diastolic function because the margin between effective afterload reduction and overt hypotension may be small. If cardiac distension occurs after weaning from bypass, rapid removal of intravascular volume may be necessary or return to cardiopulmonary bypass may be required.

Additional echocardiographic examination to discover residual lesions such as intracardiac defects or valve problems should be performed during reperfusion. As the cardiac chambers are gently filled during bypass, evidence of pulmonary hypertension should be evaluated by examining the amplitude of the Doppler jet of tricuspid insufficiency. Overt right ventricular failure is rare even in the presence of pulmonary hypertension, but leftward ventricular septal shift may compromise left ventricular function. The right and left ventricular outflow tracts and proximal great vessels should be interrogated for evidence of turbulence indicating problems with a VSD patch or arterial reconstruction. The pulmonary artery branches should be visually inspected to make sure they are not under tension. The great artery reconstruction usually places the main pulmonary artery anterior to the aorta with the branch pulmonary arteries draping to either side making recannulation of the aorta somewhat more difficult if needed after cannula removal. Complete examination of the anatomic adequacy of repair should be performed prior to decannulation.

Postoperative intensive care is typical of any neonate having cardiac surgery. Control of the inflammatory effects of cardiopulmonary bypass and the resulting coagulopathy and capillary leak, optimization of cardiac output especially in the first 8 h after reperfusion when myocardial energy stores are being normalized, and careful hemodynamic monitoring and intervention are required. Monitoring acid-base status is often supplemented by determinations of lactate levels, mixed venous oxygen saturation, and cerebral and somatic near-infrared spectrometry to assess cardiac output (De 2008; Kreeger et al. 2012; Weiss et al. 2005; Ranucci et al. 2010; Chakravarti et al. 2009). Injury currents on the electrocardiogram are abnormal and should prompt consideration of coronary insufficiency that is likely technical in origin. Temporary renal insufficiency is often seen and meticulous attention to fluid management, electrolytes, and diuresis is required. Glucose management is controversial, and although insulin is often required postoperatively for hyperglycemia, the unconfirmed benefits of "tight control" must be weighed against the risk of iatrogenic hypoglycemia to the neonatal brain (Falcao et al. 2008; Scohy et al. 2011). For some centers, leaving the sternum open for a brief time postoperatively is an institutional preference. Ventilator support is typically provided until hemodynamic stability is accomplished and sedation weaned. Although narcotics and minor tranquilizers are commonly used for postoperative sedation, emerging strategies, such as dexmedetomidine, an alpha 2 agonist, are accumulating an increasing evidence basis for use (Chrysostomou et al. 2009; Obayah

2006; Jones 2013). The use of propofol for postoperative sedation is problematic because of its deleterious effects on hemodynamic function and the rare possibility of lactic acidosis. Muscle relaxants may be used intermittently if needed in the intubated patient, but their routine or prolonged use may lead to increased incidents of failed or delayed weaning from ventilator support. Neonates who have been given muscle relaxants must be carefully assessed prior to extubation. While use of a nerve stimulator can assist with detection of residual neuromuscular blockade, neuromuscular transmission in patients less than 2 months is often immature and should not be deemed reliable unless other clinical signs of blockade recovery are present. Residual weakness is common and the duration of action of even intermediate acting agents is prolonged when given repeatedly or as an infusion, especially in the neonate and small infant whose pharmacokinetic processes are not mature.

As initial application of the arterial switch procedure progressed as an alternative to a Senning or Mustard procedure in the patient with TGA/VSD in the 1970s to its increasing application as the standard of care in the 1980s, the surgical mortality declined significantly (Cohen and Wernovsky 2006). Institutional mortality rates for simple TGA with either intact interventricular septum or with a VSD vary between 2% and 11% and often are used to benchmark the performance of a pediatric cardiac surgery program (Rudra et al. 2011). Known risk factors for increased mortality include low birth weight or prematurity, complex coronary anomalies or intramural coronary artery, concomitant LV obstruction at the conal septum or aortic arch (in patients with a VSD), and late presentation and diagnosis beyond the neonatal period. Institutional experience of the operating team, including the surgeon, anesthesiologist, and perfusionist, seems to also be related to success (Hirsch et al. 2008).

Coronary anomalies can especially affect technical difficulty and ASO success. It is important to note that coronary artery anomalies are present in greater than 30% of TGA patients and are commonly found in those with side-by-side great vessels. Overall, TGA with a variant coronary configuration can have a mortality rate double that of the usual pattern (Pasquali et al. 2002). The most common variant in TGA (comprising approximately half of these anomalies) is the circumflex artery off the right coronary artery. The most complex and dangerous patterns are rarer (1–2%); however, they carry a much greater mortality risk; patients with a single ostium had a threefold increase in mortality rate and those with an intramural course had a sixfold mortality risk (Moll et al. 2017). Overall perioperative coronary complications are now infrequent since the struggle of Jatene's early era, but it remains to be one of significant consequence. While rare, there have been successful coronary artery bypass grafts (CABG) in those with TGA with an intramural coronary course and in the young infant after ASO coronary insufficiency (Choi et al. 2021) though long-term outcomes need to be studied further. There appears to be a small number of postoperative patients (up to 10%) who have silent coronary insufficiency detected on myocardial perfusion imaging that has prompted preemptive stent intervention in the catheterization lab. These coronary problems may be related to ostial injury, late fibrosis or reactive injury to the artery, or late kinking from epicardial scarring, and their natural history is unknown (Bonnet et al. 1996; Moll et al. 2017). Adult survivors of the neonatal arterial switch have not yet commonly undergone coronary revascularization.

In addition to coronary anomalies, additional cardiac lesions (excluding VSDs), particularly left ventricular outflow tract obstruction (LVOTO) and aortic arch abnormalities are not uncommon. Up to 13% of TGA patients have coexisting arch abnormalities (hypoplastic arch, interrupted arch, or coarctation) (Latham et al. 2015); these should be explored and addressed at the same operation.

Not only are the expected short-term outcomes excellent, the long-term outcomes are much better than those seen in patients who have had a Mustard or Senning procedure (Dibardino et al. 2004). Late survival of over 90% is expected, mostly interven-

tion free (Ruys et al. 2013). Arrhythmias, heart block, and ventricular dysfunction are rare, and most patients have a normal functional class (American Heart Association) and exercise tolerance. Late follow-up of these patients is focused on the long-term fate of the main pulmonary artery and its branches and the aortic valve. Late stenosis of the pulmonary artery branches and dilation of the pulmonary artery or aortic root are described and are the focus of technical modifications of the surgical technique. Occasional reoperations to revise the aortic root or replace the aortic valve are reported (Cohen and Wernovsky 2006).

Comorbidities

TGA is rarely associated with most genetic syndromes (e.g., Turner, Noonan, Williams, Marfan, or Down syndromes), chromosome abnormalities such as trisomy 8 and 18, or anomalies involving the same embryologic substrate as the cardiac tube or branchial arches (e.g., VACTERL and CHARGE syndromes) (Ferencz et al. 1995, 1997; Bonnet et al. 1996; Marino 1996). There is an occasional infrequent association with chromosome deletion 22q11 and DiGeorge syndrome (Melchionda et al. 1995; Van Mierop and Kutsche 1986). Heterotaxy and isomerism syndromes are the only genetic syndromes highly associated with TGA (Ferencz et al. 1995).

Additional Anesthetic Considerations

The preanesthesia evaluation should focus on defining the patient's anatomic findings and the physiologic impact of those findings. Adequacy of neonatal resuscitation in patients who presented with severe cyanosis and shock should include the recovery of end organ performance such as cardiac function, renal and liver function, and assessment of any neurologic injury. The adequacy of mixing after septostomy by echocardiogram and the patient's pulse oximetry should help identify patients who have pulmonary hypertension and are significantly desaturated despite imaging evidence of an adequate ASD. This should prompt consideration of whether the expected transitional change in PVR is delayed or alternatively if an unappreciated cardiac anomaly exists that threatens the pulmonary vascular bed. If PgE is being administered, the presence of apnea or other complications of its use such as fever, hypotension, or reduced gastrointestinal perfusion pressures should be considered. In the patient with a large, widely patent ductus arteriosus and a VSD, the possibility that there is also an unrecognized coarctation of the aorta should be considered. This disastrous finding would present when the PDA is ligated at the onset of bypass as elevated resistance to flow and delayed lower body cooling on cardiopulmonary bypass and venous desaturation and metabolic acidosis despite adequate perfusion flows.

Anatomic variants that will complicate or prolong the surgical procedure or perfusion technique should be identified and considered in preoperative planning (e.g., malaligned VSD with outflow tract obstruction, aortic arch hypoplasia, or coarctation of the aorta.) Coronary artery patterns are variable in TGA and identifying the origins of the left and right coronary ostia should be done in preoperative imaging if possible. As surgical techniques for location and reimplantation of the coronary ostia evolved and the early mortality of the procedure improved, coronary anatomy is believed to not have an important impact on survival unless there is single ostial origin of both main arteries or an intramural coronary artery. Noncardiac anomalies are infrequent in TGA (except L-TGA is often associated with heterotaxy), but neonates who are premature or small for gestational age are at increased risk. Patients who were inadequately resuscitated after an unstable presentation are at increased risk. Infants who were diagnosed late, especially if they have an intact ventricular septum are especially at risk for LV dysfunction postoperatively. Persistent pulmo-

nary hypertension is an infrequent condition, but if present it increases the likelihood of ECMO support or inhaled nitric oxide being required after repair.

The anesthesiologist who has experience with infants several months old coming to the operating room for an atrial switch is often comfortable with an inhalation induction of anesthesia in patients with TGA. Also, the concept that FiO_2 and PCO_2 management may affect Qp/Qs but do not significantly change SaO_2 is reassuring when the patient's arterial saturation does not change much with induction of anesthesia. In neonates, intravenous access is usually available, and it is common to perform induction with an opioid or ketamine. The author's preference for airway management is nasotracheal intubation because fixation of the endotracheal tube is more secure, and it is more difficult for the patient to be inadvertently extubated with the manipulation of a transesophageal echo probe. Invasive monitoring catheters are routine for hemodynamic monitoring, blood sampling, and vasopressor administration. (See the " Addendum" at the end of this chapter.) Transesophageal echo probe placement is routine, and as neonatal patients are particularly susceptible to laryngeal or esophageal trauma, airway compression, and left atrial compression and hemodynamic changes from the probe, vigilance is highly encouraged. The use of antifibrinolytic agents, perfusion protocols, and preferences for inotropic medication are largely institutional preferences and their discussion in this chapter will not be undertaken.

Complex TGA

As previously discussed, simple D-TGA with and without a VSD represents the majority of cases presenting with this cardiac diagnosis, but there are specific anomalies that represent variations in anatomy that require modifications in surgical planning and procedure. These complex forms of TGA also have a short-term survival profile somewhat worse than simple transposition, and a natural history arc that is defined by more interventions and a worse long-term outcome.

TGA with Aortic Coarctation

Although TGA is rarely associated with coarctation of the aorta (4%), when a coarctation is present in a patient with TGA, it is usually in association with a VSD (Williams et al. 2003). Aortic arch hypoplasia and right ventricular outflow tract obstruction are occasionally seen. As in any patient with aortic arch obstruction, restoring the patency of the ductus arteriosus is required after birth in order to accomplish systemic perfusion. Interestingly, in TGA with a coarctation, when the ductus is reopened with PgE, the oxygen saturation of blood perfusing the lower extremities is higher than that of the right upper extremity, which is the opposite of what is seen in coarctation of the aorta with normally related great vessels (i.e., reverse differential cyanosis) (Aziz et al. 1968) (Fig. 8).

Historically, patients with TGA and aortic arch obstruction were repaired in a two-stage fashion; primary arch repair with or without pulmonary artery banding was performed followed by the arterial switch operation (Planche et al. (1993). Larger, experienced institutions have since mostly adopted the one-stage technique (Choi et al. 2016). An arterial switch and VSD repair are performed as previously described, and the aortic issue is addressed at the same time usually utilizing a brief period of deep hypothermic circulatory arrest. Usually, repair of TGA with a coarctation of the aorta and a VSD is straightforward if there is no malalignment of the VSD resulting in conal septal outflow tract obstruction of the RV or the LV. Unfortunately, there remains a high reintervention rate for right ventricular outflow tract obstructions; most of these are amenable to interventions in the cardiac cath laboratory.

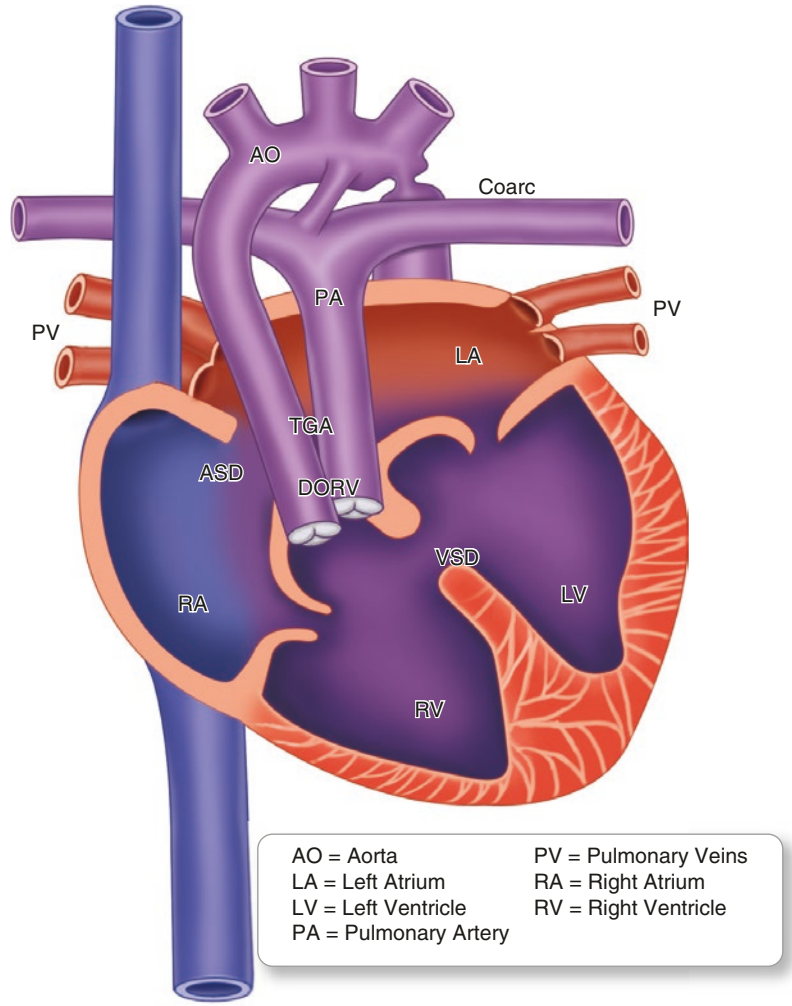


Fig. 8 TGA/coarctation of the aorta

TGA with Conal Septal Deviation

Although about a third of the 45% of all TGA patients who have a VSD do not have significant conal septal deviation, the remainder does. Therefore about 25% of TGA/VSD patients have outflow tract obstruction of either the left or right ventricle. Malalignment of the conal septum is also occasionally associated with hypoplasia of a ventricular chamber and malformation or malposition of the tricuspid or mitral valve. Preoperative surgical planning carefully considers ventricular chamber sizes, the annulus *Z*-scores and morphology of the AV and semilunar valves, and the location and the size of the VSD.

Conal Septal Deviation-TGA/VSD and LVOT Obstruction

Patients with TGA and a VSD who also have anatomic left ventricular outflow tract obstruction represent less than 10% of all patients with TGA (Williams et al. 2003). The obstruction may be related to posterior deviation of the conal septum, a discrete membrane or diffuse fibromuscular tunnel of the LVOT, straddling tricuspid valve apparatus protruding into the left ventricular outflow tract through the VSD, or complex obstruction from anomalous attachments of the mitral valve (Fig. 9).

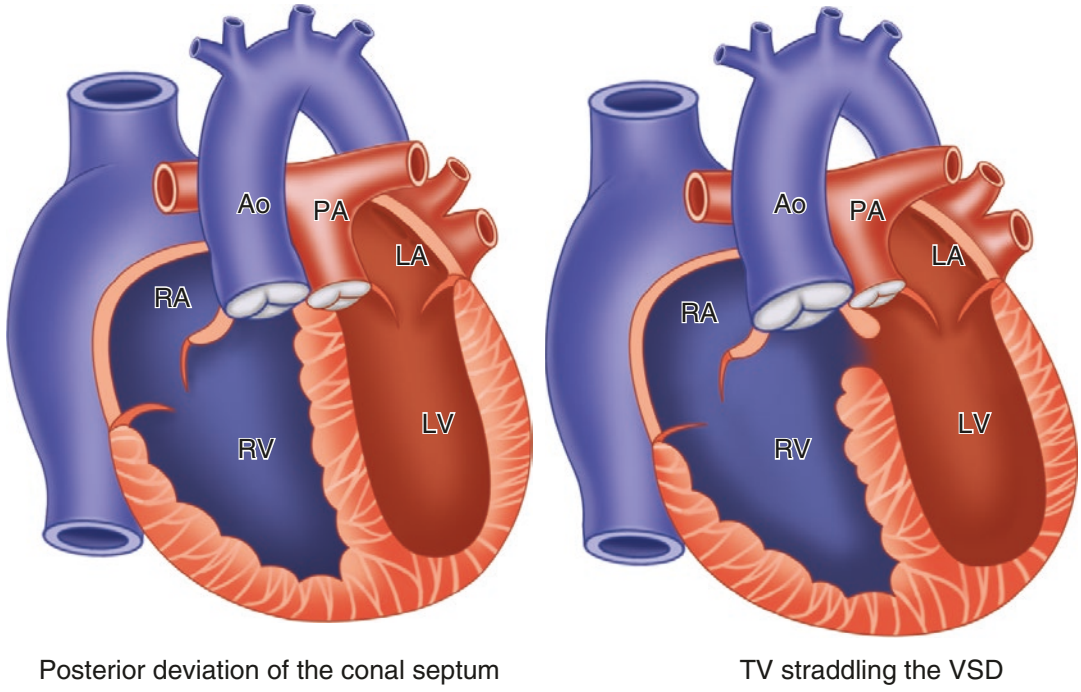


Fig. 9 TGA with LVOTO. Isolated form has no VSD. Complex form has VSD and atrioventricular valve tissue straddling the VSD

This anatomy complicates the neonatal presentation of TGA, as physiology more consistent with critically decreased pulmonary blood flow is present if the obstruction is severe, similar to patients with critical pulmonary stenosis or pulmonary atresia. Restoration of ductal patency is crucial to provide pulmonary blood flow. In cases of less severe obstruction, the typical TGA mixing physiology may be more obvious.

Palliative placement of a systemic to pulmonary shunt in the neonatal period allows delay of further surgical correction until the patient is an older infant. The most common surgical options for repair are the Rastelli procedure, the Réparation à l'Etage Ventriculaire (REV), and the Nikaidoh reconstruction.

Rastelli palliation involves enlarging the VSD and patching it so that LV blood is ejected into the aorta. The potential for developing late subaortic stenosis exists if the intraventricular tunnel to the aorta is not adequately large, and with the patient's growth, this becomes an increasing reason for reoperation. Optimal creation of the tunnel may be hampered by a small VSD, especially in the inlet position, or if atrioventricular valve tissue from either side straddles the VSD. The main pulmonary artery trunk is divided, the proximal stump oversewn, and a conduit is placed to create right ventricular to pulmonary artery continuity (Fig. 10). This also is a common cause of reintervention as the patient grows. As the RV to PA conduit functionally reduces the size of the RV, a hypoplastic RV is a relative contraindication to the procedure. Additionally, if there is an anomalous coronary artery crossing the RVOT, it may preclude placement of the conduit.

The outcome of a successful Rastelli procedure is still somewhat unsatisfying (Emani et al. 2009). The mortality of the initial procedure is as high as 7%, and the long-term freedom from reoperation poor (Mandell et al. 1990). Conduit failure occurs in 21% of patients by 15 years, and LVOT or LV tunnel obstruction is seen in 10%. The 20-year survival is as low as 59% (Dearani et al. 2001) (Fig. 11).

The Réparation à l'Etage Ventriculaire, also known as "the REV," was first introduced in the 1980s by Dr. Lecompte for repair of TGA with

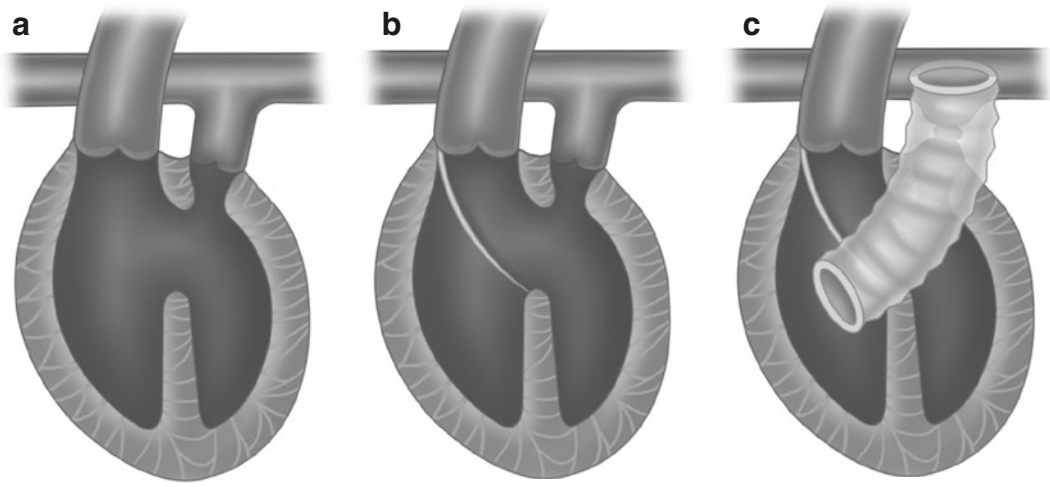


Fig. 10 (**a**–**c**) Rastelli repair of TGA/VSD/LVOTO

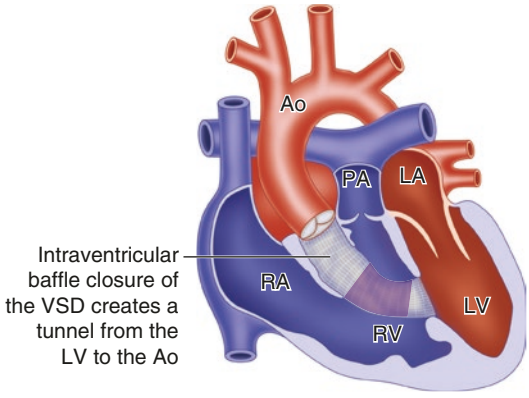


Fig. 11 VSD baffle in Rastelli repair

LVOTO as an alternative to the Rastelli procedure. Its goal was to circumvent the limitations that plagued the Rastelli: conduit failure and late subaortic stenosis. The procedure involves directly implanting the RV to the pulmonary trunk (thereby avoiding the use of a conduit) and extensively enlarging the conal septum (to prevent LVOTO) (Brown et al. 2011). The REV showed improved survival compared to the Rastelli procedure; the 25-year survival was 85% and freedom from reoperation was 45% (Di Carlo et al. 2011). Neither the Rastelli nor the REV involve reimplanting the coronary arteries, which is typical in the Nikaidoh and Jatene's arterial switch operation.

The Nikaidoh procedure translocates the aortic root from the right ventricle to the left ventricle and reconstructs both the left and right bulboventricular outflow tracts (Nikaidoh 1984). Because the entire aortic root, with its coronaries, is translocated en bloc, the aortic valve is restored to its systemic position (in the Nikaidoh, the new RVOT is usually valveless); in contrast, the ASO involves a supravalvular switch but keeps native aortic valve in a lower-pressure system and the native pulmonary valve exposed to a higher-pressure system (Hu et al. 2008). Execution of the Nikaidoh procedure in a patient with complex coronary anomalies—once thought to be contraindicated—is a meticulous undertaking that could easily render coronary arteries to kink and become ischemic. This technically demanding operation restores a nearly anatomically correct heart and avoids the use of a conduit to connect RV to PA (Morell et al. 2005); instead, a homograft or patch is utilized to reconstruct the RVOT. Although not widely applied, a mortality rate of 5% is reported for this operation from a few centers. Freedom from reoperation is overall excellent (Yeh et al. 2007) (Figs. 10, 11, and 12), with most reinterventions involving the aortic valve for insufficiency and RVOTO (Hazekamp et al. 2018).

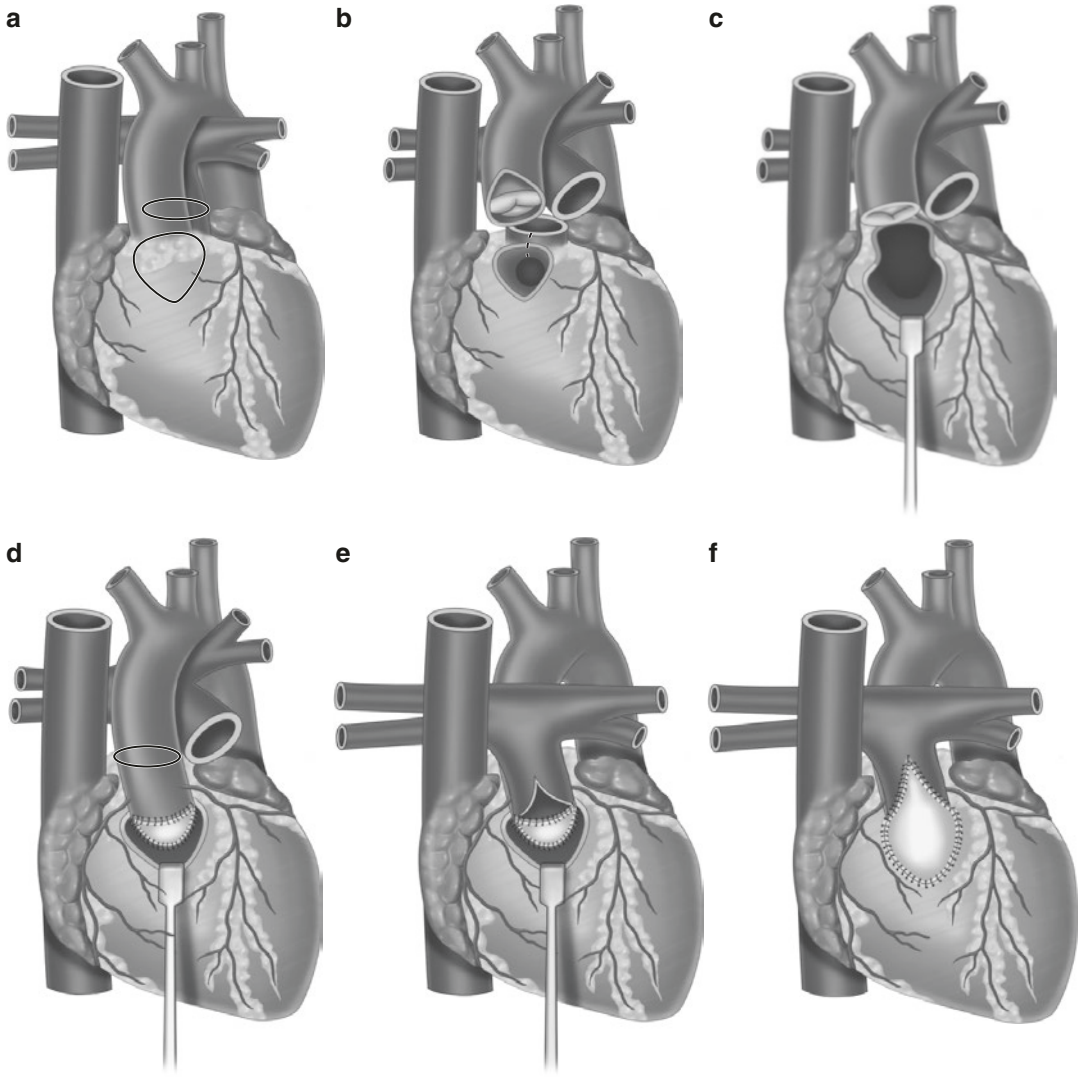


Fig. 12 (**a**–**f**) Nikaidoh procedure

Conal Septal Deviation-Taussig Bing Anomaly

Double outlet right ventricle has several anatomic variants where the specific position of the VSD defines distinct physiology. For example, when the VSD is subaortic, the patient is typically overcirculated and in high-output heart failure, and arterial saturations are nearly normal. Sometimes there is coexisting pulmonic stenosis, which typically prevents pulmonary overcirculation, and its physiology is similar to the Tetralogy of Fallot (DORV Tet-type). When the VSD is subpulmonic and the aortic and pulmonary annuli are in a side-by-side arrangement, it is called the Taussig-Bing anomaly (Fig. 13). The physiology is similar to that of transposition of the great vessels and is defined by mixing of oxygenated blood from the LV streaming through the VSD into the pulmonary artery, while desaturated blood streams into the aorta. Often the streaming patterns preclude adequate mixing and saturations are typically very low despite adequate pulmonary blood flow and an anatomically large VSD.

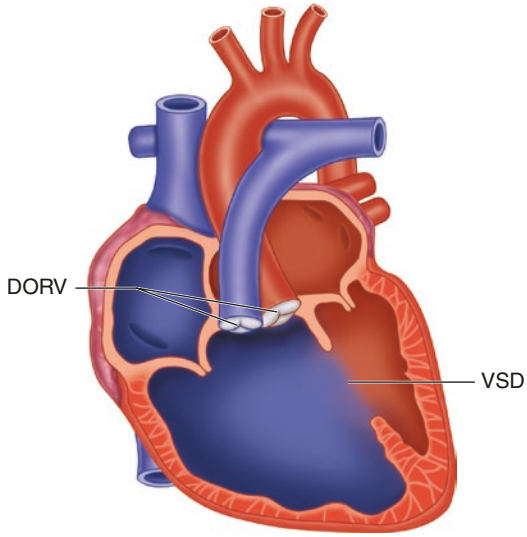


Fig. 13 DORV

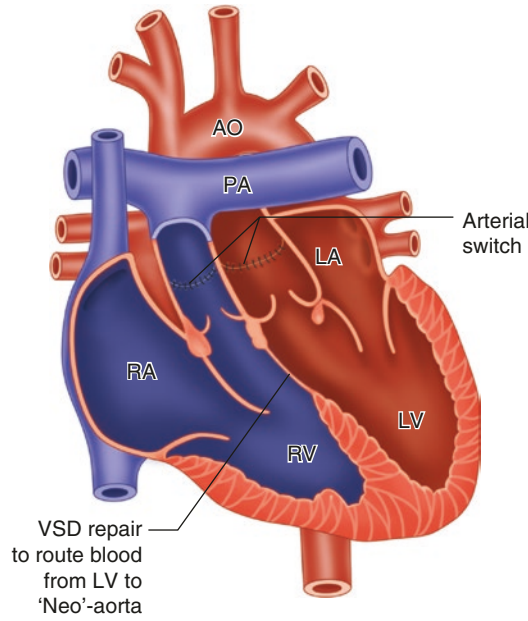


Fig. 14 DORV/arterial switch

In contrast to simple TGA where the additional presence of coarctation is rare, about 50–54% of Taussig-Bing anomaly patients have aortic arch obstruction (Comas et al. 1996). Because the subpulmonic VSD receives much of the left ventricular output (and is delivered out the PA), this was thought to contribute to aortic arch obstruction and subaortic stenosis (Luo et al. 2017). Restoring ductal patency in these patients may be required.

The intracardiac defect in Taussig-Bing anomaly is repaired by creating an intraventricular tunnel from the LV to the aorta if the location of the aorta in relation to the interventricular septum is favorable or by arterial switch operation if the distance between the LV and the aorta is remote (Fig. 14). The arterial switch has been used successfully in patients with side-by-side and anterior-posterior relationships of the aorta and pulmonary artery (Rodefeld et al. 2007). It is also combined with aortic arch reconstruction when arch obstruction is present. Taussig-Bing anomaly patients with aortic arch obstruction can develop pulmonary hypertension at an accelerated rate due to the increased pulmonary blood flow and should be repaired in the first few months of life. The short-term survival for TB is 90%, and although the 15-year survival is 85–89%, there are a small number of patients who require reoperation for residual aortic arch obstruction or recurrent RVOT obstruction (Alsoufi et al. 2008).

Corrected Transposition of the Great Arteries

Corrected transposition is a rare type of TGA with both atrioventricular discordance and ventriculoarterial discordance (Allen et al. 2001b) (Fig. 15). The atria are usually situs solitus, but the ventricles, and its corresponding atrioventricular valves, are inverted. The right-sided mitral valve and right-sided morphologic left ventricle receive deoxygenated blood from the right atrium and eject out the pulmonary artery. The left-sided tricuspid valve and left-sided morphologic right ventricle are on the systemic side and eject fully oxygenated blood out the aorta.

There are no specific symptoms referable to the defects in segmental arrangement in the infant unless there are additional cardiac anomalies. Over time, the tricuspid valve and left-sided morphologic right ventricle may struggle to continue to perform as the systemic duo.

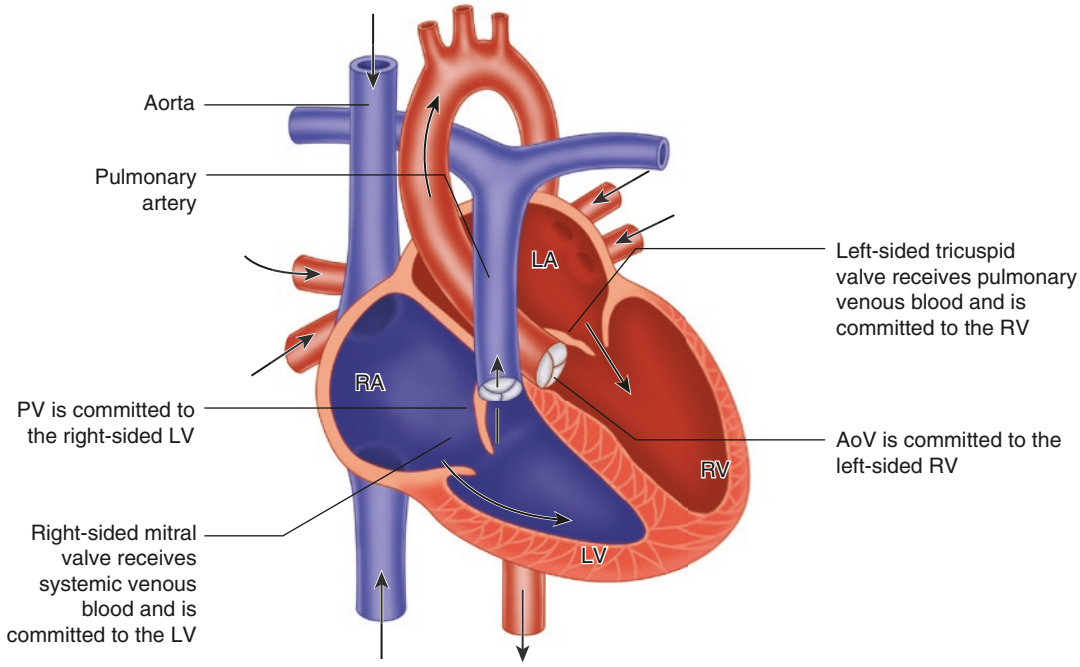


Fig. 15 Corrected TGA

As a result, the defect may not present until later in life when severe tricuspid regurgitation, dysrhythmias, or heart failure manifest.

Cardiac variations of corrected TGA are common. Most patients (60–80%) have a large VSD associated with a large left-to-right shunt. Many patients (30–50%) have obstruction to pulmonary blood flow from fibromuscular LVOT obstruction (LVOTO). If LVOT obstruction and a VSD are both present, there can be cyanosis with right-to-left shunting, especially if the VSD is maligned. This physiology is similar to tetralogy of Fallot.

Approximately one-third of corrected TGA patients have an Ebsteinoid malformation of the systemic atrioventricular valve (Kumar 2020), wherein the valve is inferiorly displaced into the right ventricle. These patients are likely to have a much earlier onset of heart failure.

Abnormalities of atrioventricular conduction are also seen (Wallis et al. 2011). The location of the SA node is normal in these hearts just lateral to the junction where the superior vena cava enters the right atrium, but the AV node is positioned beneath the right atrial appendage instead of the posterior inferior area of the interatrial septum near the coronary sinus. The course of the long bundle that divides the right bundle branch leftward to the morphologic right ventricle and the left bundle to the right-sided left ventricle is markedly abnormal. Patients with corrected TGA have a 10% incidence of complete heart block at birth. Even if they have normal conduction, heart block is still progressive and increases at a rate of 2% per year (Baruteau et al. 2017). By adolescence up to 15% have heart block, and by 45 years of age, 30–50% of patients have heart block (Anderson et al. 1973; Huhta et al. 1983).

Presentation of patients with corrected TGA is related to the presence or severity of the above associated cardiac lesions. In the absence of these, most infants and young children are not symptomatic (Presbitero et al. 1995). Patients usually come to early diagnosis if they have a large VSD and acyanotic heart failure, a VSD with LVOTO to pulmonary blood flow with cyanosis, or heart failure in association with tricuspid valve regurgitation. Likewise, early diagnosis

is facilitated in the neonate if there is a PDA-dependent lesion such as severe coarctation of the aorta. While aortic arch abnormalities are overall uncommon in corrected TGA patients, they tend to be associated with those who have an Ebsteinoid systemic atrioventricular valve (Celermajer et al. 1991).

Surgical repair of septal defects, resection of outflow tract obstruction in the right-sided left ventricle, and pacing interventions are often done in children with corrected transposition. These physiologic repairs keep the right ventricle and tricuspid valve as the systemic duo, however, and surgical injury to the abnormally located conduction tissue is common (De Leval et al. 1979). Surgical outcome is worse with higher operative mortality and lower 10-year survival estimates than similar repairs in otherwise normal hearts (Ibrahimiye et al. 2016).

With or without concomitant cardiac lesions, the long-term survival of patients with corrected transposition is most related to the inevitable progression of tricuspid valve dysfunction and systolic failure of the left-sided right ventricle. The predictable failure of the anatomy of corrected transposition is a manifestation of the lack of durability of right heart structures when located in the systemic rather than the pulmonary circuit (Peterson et al. 1988). Although tricuspid valve replacement is occasionally performed, the only surgical therapy in the setting of end-stage congestive cardiomyopathy is cardiac replacement. Some corrected TGA patients may be deemed "unseptatable," such as those with a large VSD, wherein anatomical repairs may not be possible. Conversion to single ventricle physiology with total extracardiac cavopulmonary shunt is a possibility for these patients; however, a well-functioning atrioventricular valve is still necessary. Additionally, the sequelae of long-term Fontan circulation are not without its own concerns. Because there has been a recent surge in enthusiasm for anatomic repairs, there is insufficient data to reveal whether a Fontan pathway in the corrected TGA patient is superior or not to the anatomically corrected pathway (Karl 2011).

The preemptive treatment of corrected transposition has been investigated and indications for surgical intervention are evolving. The argument that the natural history of the failing left-sided AV valve and ventricle leads to early death or cardiac transplantation is a compelling reason to consider alternative surgical therapies that might avoid those endpoints. Anatomic correction can be accomplished by an arterial switch procedure combined with a Senning atrial switch (ASO/Senning or "double-switch") (Brawn 2005) (Fig. 16). This restores the morphologic left ventricle and mitral valve on the right side of the heart to function as systemic structures and the morphologic right ventricle and tricuspid valve on the left side of the heart to function as pulmonary structures.

Many advocate ASO/Senning as indicated in the younger child who is having symptoms from RV failure or tricuspid valve insufficiency (Jahangiri et al. 2001). Unlike the patient with no symptoms and no associated cardiac lesions, the short-term outcome for these patients without intervention is immediately poor. Regardless of whether an ASO/Senning is performed on a symptomatic or an asymptomatic patient, it is unknown at this time whether this extends the life expectancy of the patient or simply changes the problems occurring in the natural arc of their cardiac disease. Answering these questions is difficult because of the rarity of the condition compared to other cardiac anomalies. Also confounding the analysis is the problem that prior to an ASO/Senning, the right-sided left ventricle must be reconditioned, and although this may be accomplished with a pulmonary artery band (PAB), the process of increasing LV myocardial muscle mass over time is unpredictable. Another variable is that the older the patient, the more ineffective LV remodeling may be (Quinn et al. 2008). In a neonate or young infant, retraining as evidenced by MRI estimation of LV muscle mass, LV wall thickness, and LV pressures may occur in a few months; in the older child, the time required is less predictable. Not all patients survive PAB preparation of the LV or demonstrate an appropri-

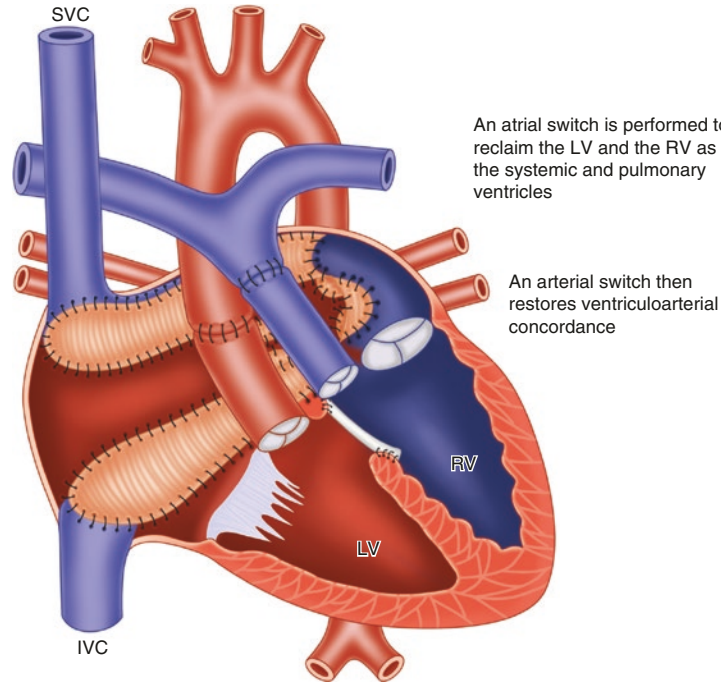


Fig. 16 Arterial switch/Senning for corrected TGA

ate response to the procedure to further undergo ASO/Senning repair (Winlaw et al. 2005). Some centers report a 90% 10-year survival for small series of patients who undergo PAB and then ASO/Senning. These promising results may be misleading in that this group is favorably selected because patients who failed to successfully endure LV retraining are not included. Late ventricular dysfunction is known to occur after apparently successful ASO/Senning resulting in far less successful long-term outcomes. Identifiable risk factors for poor outcome are preoperative RV failure or tricuspid insufficiency. Even if RV ejection fraction is maintained preoperatively, RV dilation with end-diastolic dimensions (RVEDD) greater than 60 mm is associated with significant mortality (Deng et al. 2018).

Current trends in the application of the ASO/Senning strategy for avoiding cardiac failure in patients with corrected transposition support doing the procedure prior to the onset of tricuspid insufficiency and ventricular dysfunction. Unfortunately, many of these patients are not yet diagnosed. Even when there is a diagnosis, the procedure is inherently risky with a 10% mortality rate and this may not be acceptable to asymptomatic patients. Comparing the 90% survival reported by a few centers to a cohort of like patients who are asymptomatic and do not undergo surgery is difficult because the cardiac defect is rare (Sano et al. 1995; Gaies et al. 2009). When endpoints such as persistent tricuspid valve problems, need for atrial baffle revision, need for reoperation on the pulmonary valve or pulmonary artery, neoaortic valve incompetence, and impaired LV function are considered, it becomes obvious that the ASO/Senning type anatomic correction is applicable to a complex set of patients who continue to have difficult issues after surgery and frequently require reoperation (Voskuil et al. 1999). It seems that the important natural history issues of tricuspid insufficiency and heart failure are not resolved and are replaced by an even longer list of adverse potential problems. Therefore, anticipation that the "double-switch" procedure is predictably successful for symptomatic or asymptomatic patients is speculative and not supported by large data sets at this time.

Addendum on Invasive Monitoring Catheter Insertion: Author's Opinion

As many of the cardiac lesions discussed require operative repair while the patient is a neonate or infant, the subject of invasive monitoring catheter placement is pertinent. Invasive arterial and central venous monitoring catheters have long been an expected skill of the pediatric cardiac anesthesiologist, and the literature guiding their use and various insertion practices is varied and controversial. The authors' bias based on literature and personal experience is that success rate and complication profile of arterial and central venous catheter insertion improves with operator experience and "procedural self-awareness". The exception to this caveat is the infrequent but disastrous ischemic complication of a lower extremity due to femoral artery catheterization in an infant or small toddler, where ischemic events seem to be unpredictable and episodic, mainly related to the patient's size. Serious ischemic injury due to a femoral artery catheter in an infant or small toddler occurs more frequently than when peripheral arterial sites are used; therefore, it seems reasonable to use the femoral artery as infrequently as possible in these patients (Gleich et al. 2021).

Ultrasound for Central Venous Line (CVL) Placement and Arterial Cannulation

Ultrasound has provided an anecdotal but not evidence-based impact on the incidence of some complications. When ultrasound first became widely used in central catheter placement in the 1990s, it appeared that its greatest benefit was to the low-volume proceduralist. Emerging data over the subsequent decades may evolve differently because the number of practitioners with high-volume experience without the use of ultrasound has decreased. Trainees taught CVL cannulation with ultrasound often do not have a nuanced appreciation of the relevant surface landmarks.

Ultrasound used to visualize puncture of a central vein or to verify wire placement after puncture seems intuitively useful. However, ultrasound does not reduce to zero complications such as inadvertent arterial puncture. Placement of central catheters into the arterial circulation still occurs, and the complete loss of control of the Seldinger guidewire into the catheterized vessel is still occasionally seen.

The evolving use of ultrasound in arterial cannulation also has not reduced to zero the complications of insertion. Wire disruption of the arterial intima with failed cannulation of the artery seems to be related to operator skill and is independent of ultrasound visualization. Arterial vessel avulsion or arterial thrombosis can occur despite the use of ultrasound. The use of the ultrasound to visualize an artery that is small and cannot be palpated may paradoxically lead to an ischemic complication that wouldn't have occurred had a larger artery been chosen. Line placement remains a tactile skill irrespective of the advantages of ultrasound visualization of the vessel. Some of the authors' guiding principles (opinions) are presented:

1. Arterial site selection should preferably be a peripheral artery with collateral circulation, especially in the infant. Allen tests are difficult to interpret in an infant. In the upper and lower extremity, the radial artery is usually larger than the ulnar artery, and the posterior tibial artery is larger than the dorsal pedal artery. In a premature infant, the posterior tibial artery is larger than the radial artery. Thrombosis after use in infants is common but of little consequence as long as the collateral artery is intact. Unfortunately, atraumatic insertion is difficult for the inexperienced practitioner; the authors' strong bias is that cutdown technique (without ligation of the artery) in the neonate is preferable and more successful than percutaneous technique. The goal over many thousands of placements is to reduce the number of unsuccessful attempts as much as possible and make successful cannulations with as little trauma as feasible.

Failed cannulations often damage the artery making a subsequent attempt at cannulation more likely to be complicated. Placement of the catheter in the artery under direct vision rarely requires a guidewire and in the authors' opinion is the least traumatic way to cannulate the artery in an infant. Fellows and attending faculty in the authors' cardiac training program have successfully acquired the skill of radial and posterior tibial artery cutdown when carefully mentored. The additional benefit of a small scar from previous cutdown is that the site is identified as having been previously used and can be avoided in the future. If a percutaneous approach to a peripheral artery is undertaken (with or without ultrasound), the use of an IV catheter in a through-and-through puncture and slow withdrawal of the catheter until arterial pulsations are observed, and then careful placement of a small straight guidewire prior to advancing the catheter is associated with a high success rate.

2. Once a peripheral site in an infant has been used or attempted, it should not be reused in the immediate future. Neither should the collateral artery to the same limb be used/attempted.
3. The femoral artery should be avoided when possible in infants and small toddlers as the incidence of major ischemic injury is much higher prior to the age of 2–3 years. Early and late ischemic complications are reported. Late presentation of leg length discrepancy due to ischemia of the femoral growth plate is possible and is unappreciated at the time of catheterization. When the femoral artery is cannulated, the size of the catheter is important, and an atraumatic insertion technique is essential. If an acute ischemic complication with potential tissue loss occurs, an algorithmic approach to diagnosis and treatment is required. It is unclear that the use of ultrasound changes the complication profile of femoral arterial catheters in infants, although it may improve the likelihood of insertion. In patients over the age of 3 years, the careful use of the femoral artery is associated with a much safer complication profile.

The difficulty that the above recommendation obviously poses is that many pediatric anesthesiologists are not experienced enough to perform peripheral artery cannulation in an infant with a high success rate, and the decision to cannulate the femoral artery is made because it is technically more feasible. The operator who only occasionally places arterial lines in infants may not appreciate the increased risk of the technique because of their low volume of procedures; nonetheless, the risk is still high. Skill at peripheral cannulation with ultrasound guidance if needed or with cutdown technique is strongly encouraged.

4. Novel arterial sites such as the brachial artery or axillary artery are reported as routine by some institutions that also cite low complication rates. However, these approaches put the limb at risk due to the unknown amount of collateral circulation, and have the further disadvantage of both being close to neural structures.
5. The Seldinger technique is just as valuable for percutaneous arterial cannulation as it is essential for central venous catheterization. But if the wire doesn't advance very easily, there's a problem to be solved. (Withdrawing a guidewire through an insertion needle may shear the wire; the wire and needle should be removed as a unit. If it has been introduced via an IV catheter, removal is usually uneventful.)
6. There are separate complication profiles for internal jugular versus subclavian approaches to central venous cannulation. Subclavian catheters require care in insertion in patients having median sternotomy to avoid kinking the catheter; a common technical problem is to puncture the costoclavicular ligament during insertion. The insertion site should be lateral to the ligament and caudad enough to avoid the catheter kinking under the clavicle when the sternal retractor is in place. Left subclavian cannulation in infants is easier as the path of the guidewire into the SVC is more gradual than if approached from the right. In cardiac procedures, the occasional inadvertent

violation of the pleura is rarely consequential as it is easily identified after median sternotomy. The occasional malposition of the subclavian catheter into a jugular vein may be suspected by resistance to the wire passing beyond the distance from the insertion site to the jugular bulb and the failure to elicit an arrhythmia with the wire. If the catheter is placed in the jugular instead of central circulation, the pressure recorded is higher than expected and external compression of the jugular vein in the sternocleidomastoid triangle at the base of the neck causes it to rise further. The optimal position of the tip of the catheter in the SVC or the right atrium is largely situation dependent and is easily adjusted by the surgeon trimming the catheter after right atriotomy.

7. Wire placement during CVL placement should be very easy and it may be useful to elicit an arrhythmia (except in high-risk conditions where ventricular fibrillation is likely), confirming venous placement. It is very difficult to cross the aortic valve retrograde with the guidewire in the event of inadvertent arterial puncture. Wire position is reliably determined by ultrasound if needed. Dilator placement should be only so far as to enlarge the puncture hole of the vein and should meticulously follow the path of the wire without distorting the path or else the wire can be easily bent. (A bent wire should be exchanged through an IV catheter.) Except when cannulating the femoral vein or right internal jugular vein, there is substantial risk of caval perforation by advancing the dilator too far.
8. In infants the risk of severe thrombosis of the great vein is increased and is related to many factors. It is likely that cannulation of the right internal jugular vein puts less of the upper extremity venous system at risk compared to the left internal jugular or either subclavian vein.
9. If there is a known persistent left superior vena cava (LSVC), there may be some merit in avoiding cannulation of the left subclavian or jugular veins. The course on the chest X-ray of a CVL catheter in the LSVC appears "arterial," and the cava often ends in the coronary sinus, so a thrombotic complication has severe implications for coronary circulation. An unsuspected LSVC encountered while attempting a left subclavian access has a different tactile feel as the guidewire makes a caudad turn just proximal to the left sternal border. If the operator doesn't recognize this and advances the dilator too aggressively, the cava may be perforated.

Despite the increasing use of ultrasound to improve the success and safety of arterial and venous access procedures, it seems likely that the operator's experience, attention to detail, accumulative learning, and "procedural awareness" skills remain the most important considerations to minimizing the likelihood of the most major complications of invasive monitoring catheters and reducing the incidences of minor complications and failed attempts.

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Truncus Arteriosus

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Abstract

Persistent truncus arteriosus, also known as truncus arteriosus, is one of the cyanotic congenital heart diseases with the following main characteristics: ventricular septal defect (VSD)—either complete or partial, a common ventricular outflow tract, and a single valve at the common truncal output. Regarding embryologic sources, the conal septum formation is not complete in these patients, and deficiencies in neural crest development result in persistent truncus arteriosus. There are two main known classification systems used to classify truncus arteriosus. The Collett and Edwards classification subdivides truncus arteriosus into type 1 to type 4. However, Van Praagh and Van Praagh have offered a modified classification in truncus arteriosus from type A1 to type A4. Jacobs, et al. have expanded Van Praagh's classification. Prenatal diagnosis is performed in most cases between 20 and 25 weeks, using fetal echocardiography. In these patients, these three circulation beds affect the global outcome: systemic blood flow, pulmonary blood flow, and coronary blood flow. The main goal in intraoperative anesthesia management is to create a delicate balance between the pulmonary blood flow and the systemic blood flow (i.e., Qp/Qs) and also, to maintain coronary perfusion. The main goals of surgical repair are separation of systemic and pulmonary circulation, closure of the ventricular septal defect (VSD), establishing a right ventricle to pulmonary artery pathway, and correction of any associated cardiac lesions.

Keywords

Persistent truncus arteriosus · Ventricular septal defect · Van Praagh's classification
Congenital heart disease · Anesthesia
Cardiac surgery

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Introduction

Persistent truncus arteriosus, also known as truncus arteriosus (TA), is one of the cyanotic congenital heart diseases with the following main characteristics (Bhansali and Phoon 2021):

1. Ventricular septal defect (VSD; either complete or partial).
2. A common ventricular outflow tract.
3. A single valve at the common truncal output.

This is a relatively rare disease with an incidence of about 1–3% of the total congenital heart disease patient population.

This defect is characterized by a normal pattern of atrial arrangement and connections and concordant atrioventricular connections, draining into a common arterial trunk; the latter receives blood from both ventricles and perfuses the same blood to the systemic and pulmonary trunk and the coronary arteries. Without complete early repair (usually within the first 2 weeks after surgery), there is a very high chance of mortality with a 75% mortality rate within the first year of life (McGoon et al. 1968; Ruan et al. 2016; Peter et al. 2019; Naimo and Konstantinov 2021). If the pulmonary vascular resistance (PVR) increases to more than 8 Wood units or the patient has Eisenmenger's syndrome, any surgical repair in patients older than two years of age would be contraindicated (Ziyaeifard et al. 2014). In very rare cases, some patients might survive until the fourth decade of life (Abid et al. 2015; Ruan et al. 2016; Peter et al. 2019).

Embryology

Truncal ridges form in the truncus arteriosus during the 5th week of gestation. These truncal ridges become continuous with the conal septum superiorly and eventually fuse to separate the truncus arteriosus into two channels, the aorta, and pulmonary artery. The spiral formation of these ridges results in the normal orientation of the aorta and pulmonary artery. The conus gives rise to the left and right ventricular outflow tracts when the conal septum formation is complete. The truncal and conal septum then fuse, creating the right ventricular to the pulmonary artery and left ventricular to aortic continuity. Therefore, persistent truncus arteriosus results from the failure of the truncal ridges and aortopulmonary septum to develop and divide into the aorta and pulmonary trunk (Kloesel et al. 2016; Farraj and Zeltser 2021; Rosen and Bordoni 2021).

The mechanism for failure of the truncal septation is not clear. In experimental studies, outflow tracts are created when the conal septum formation is complete. The truncal and conal septum then fuse, creating the right ventricular outflow tract to the pulmonary artery and left ventricular outflow tract to the aortic continuity. Therefore, persistent truncus arteriosus results from the failure of the truncal ridges and aortopulmonary septum to develop and divide into the aorta and pulmonary trunk (Kelly et al. 2014; Farraj and Zeltser 2021).

The mechanism for failure of the truncal septation is not clear. Several experimental studies have shown that deficiencies in neural crest development result in persistent truncus arteriosus. The neural crest also develops into the pharyngeal pouches which then develop into the thymus and parathyroid glands. This explains the association of truncus arteriosus with DiGeorge syndrome or chromosome 22q11 microdeletion; in fact, about 40% of TA patients have 22q11 deletion in their chromosomes (Ziyaeifard et al. 2014; Pierpont et al. 2018). However, in recent years, other genes like GATA6, NKX2.6, TBX20, SALL1, NKX2–6, and other variants in NKX2–5, GATA6, DGCR6, DGCR8, TBX1, and ACTA2 have been proposed as potential factors in the development and/or the course of the disease (Huang et al. 2017; Pierpont et al. 2018; Du et al. 2019; Diz et al. 2021).

In addition, multiple studies have demonstrated this association with other conotruncal anomalies. These studies have found a higher incidence of complex cardiovascular defects with depressed immunologic status, neonatal hypocalcemia, pulmonary vascular reactivity, bronchomalacia and bronchospasm, laryngeal abnormalities, behavioral feeding difficulties, risk of aspiration, neuropsychological abnormalities, difficulties in swallowing, and a tendency towards airway bleeding (Arena 2011; Maldjian and Sanders 2018; Unolt et al. 2018; Diz et al. 2021).

Classification

There are two main known classification systems used to classify truncus arteriosus. Anatomic classifications have been based on the pulmonary artery origin from the common trunk.

The Collett and Edwards classification subdivides truncus arteriosus into 4 types (Collett and Edwards 1949; Russell et al. 2011; Bhansali and Phoon 2021):

- Type 1—there is a single common trunk leading to both aorta and a short main pulmonary artery which is in the left of the common trunk.
- Type 2—both right and left pulmonary arteries originate together from the dorsal wall of the common trunk; however, they are closely positioned.
- Type 3—there are one or two pulmonary arteries which arise from each side of the common trunk; they are independent.
- Type 4—pulmonary arteries arising from the descending aorta.

However, Van Praagh and Van Praagh have offered a modified classification in truncus arteriosus (Van Praagh and Van Praagh 1965):

- Type A1—similar to type 1 Collett and Edwards; there is a shared common arterial trunk for both aorta and main pulmonary artery.
- Type A2—combines types 2 and 3 Collett and Edwards.
- Type A3—describes a single pulmonary artery origin from the truncus with either a ductus or collateral vessels supplying the contralateral side.
- Type A4—truncus arteriosus seen in association with an interrupted aortic arch.

Jacobs, et al. have expanded Van Praagh's classification to allow for all variants and associated anomalies of truncus arteriosus.

Anatomy and Associated Anomalies

Truncus arteriosus is a single great vessel arising from a common semilunar valve or truncal valve. The truncal valve is often insufficient owing to abnormally thickened and deformed leaflets. It is rarely stenotic. The truncal valve is tricuspid 60% of the time, quadricuspid 25% of the time, and bicuspid 5%. The ventricular septal defect is malaligned to the right. It is usually located in the anterosuperior position remote from the conduction system (Naimo and Konstantinov 2021).

Anomalous origin and distribution of coronary arteries can be seen in truncus arteriosus. Common origins of the left and right coronary artery have been reported in addition to abnormally high osteal takeoffs above the sinuses of Valsalva; the anatomy of the coronary origins is quite variable and depends on the number of leaflets found on the truncal valve; if the truncal valve has three leaflets, the coronary anatomy pattern would be near-normal; whatever the morphology, the right coronary artery is the dominant one in most cases (de la Cruz et al. 1990; McElhinney et al. 2000; Baraona et al. 2012).

The aortic arch can be right-sided in 20–35% of patients with truncus arteriosus and is usually associated with mirror-image branching of the brachiocephalic arteries (Law and Mohan 2021). A patent ductus arteriosus is sometimes encountered and may be associated with an interrupted aortic arch which is seen in up to 15% of patients with truncus arteriosus (Tlaskal et al. 2005; Konstantinov et al. 2006).

Other defects of surgical significance include persistent left superior vena cava, atrial septal defect, and anomalous subclavian artery. Noncardiac anomalies are present in about 20% of cases which can contribute to mortality. DiGeorge syndrome is associated 30% of the time. Less common cardiac defects such as tethered-cord syndrome, unilateral renal agenesis, and anal atresia can be seen (O'Byrne et al. 2014; Pierpont et al. 2018).

Diagnosis

Prenatal diagnosis is performed in most cases between 20 and 25 weeks, using fetal echocardiography, which is highly dependent on the clinical skills of the operator; novel techniques such as 4D ultrasonography significantly improve the quality of the imaging (Gotsch et al. 2010). Clinical diagnosis includes general findings including some degrees of cyanosis (less in severity than a transposition of great vessels), failure to thrive (FTT), findings related to heart failure, and respiratory infection or respiratory distress. However, the diagnosis is often made by echocardiography; other studies like cardiac MR imaging and/or computed tomography (CT) angiography may possibly add more data. On the other hand, there is no usual indication to use angiography in TA patients (Koplay et al. 2014; Sharma et al. 2016).

Natural History

Before birth, the systemic and pulmonary vascular resistance are not significantly different, and the blood flow to these two vascular beds is equal. During fetal life, truncus arteriosus does not impose a major pathophysiologic burden on the body as the source of fetal organ oxygenation is not from the lungs. However, during the early minutes after birth, there is a rapid drop in pulmonary vascular resistance due to the direct oxygen delivery to the lung parenchyma. This leads to a significant prompt drop in normal pulmonary circulation. However, in the truncus patients, the common blood flow to the systemic and pulmonary vasculature leads to a very high systolic and diastolic blood flow to the lungs. If the presence of an insufficient common valve existed between the ventricles and the common arterial trunk, this would lead to an increased retrograde blood flow during diastole which both increases the pulmonary vascular flow and decreased coronary blood flow; adding to the latter, the increased filling load of the ventricles in diastole leads to an increased chance of myocardial ischemia. "Diastolic runoff" could significantly jeopardize the coronary blood flow which is mainly diastolic perfusion. So, TA patients are at great risk of myocardial perfusion instability and myocardial ischemia due to some series of physiologic events:

- Low diastolic pressure in the truncus,
- Blood drainage from the systemic to the pulmonary arterial tree,
- Diastolic regurgitation in case of insufficient TA valve,
- High end-diastolic pressure in the ventricles,
- Pulmonary over-circulation from the other side.

These events can easily aggravate the fate of the TA patients with acute cardiac decompensation, the resulting heart failure, and myocardial ischemia (Ziyaeifard et al. 2014; Bhansali and Phoon 2021).

In TA patients, three circulation beds affect the global outcome:

- *Systemic blood flow*: impaired systemic perfusion especially in the diastole; like CNS and viscera; increased chance of necrotizing enterocolitis in TA infants could ensue.
- *Pulmonary blood flow:* increased flow due to the left to right shunt.
- *Coronary blood flow:* during diastole may be jeopardized due to the "diastolic runoff".

Perioperative Evaluation and Management

Truncus arteriosus is a rare but critical congenital heart defect. Most patients are diagnosed within the first few days of life and will have some degree of hypoxia due to a significant increase in pulmonary blood flow and heart failure. However, perioperative considerations vary regarding the patient's age and anatomy at appearance. Without surgery, the average life expectancy of patients with TA is less than 6 months (Ziyaeifard et al. 2014; Parikh et al. 2018).

Preoperative Assessment and Preparation

As with any surgery, preoperative evaluation begins with a review of medical and prenatal history and detailed physical examination. Because of the association with 22q11deletion syndrome, patients should be evaluated for hypocalcemia and craniofacial disorders that affect the upper airway (McDonald-McGinn et al. 2015; Campbell et al. 2018; Unolt et al. 2018; Mille and Shankar 2020). Due to the high risk of pulmonary over-circulation and congenital heart failure (CHF), neonates with TA must be assessed for tachypnea, tachycardia, use of the accessory respiratory muscles, and hepatomegaly.

Patients with TA have a bounding pulse secondary to sudden drainage of blood from the aorta to the pulmonary artery during diastole and the resulting increased systemic pulse pressure. Cyanosis is usually mild, and oxygen saturation may improve in the first few days of life due to reduced PVR (Vohra et al. 2010; Bhansali and Phoon 2021).

Even in patients with an underlying interrupted aorta, arterial oxygen saturation in pre- and post-ductal is not much different since mixing of blood occurs at the level of the ventricle and common arterial trunk, therefore, "differential cyanosis" is not a finding in TA. Additionally, blood pressure is not usually different between the upper and lower extremities because the ductus arteriosus in these patients is large enough, and it is very unlikely to be closed even in the absence of prostaglandin infusion; however, some patients with Van Praagh type 3 or type 4 truncus arteriosus may have systemic or pulmonary ductus-dependent blood flow and, therefore, require a PGE1 infusion, although most remain open without prostaglandin infusion (Vohra et al. 2010; Mille and Shankar 2020).

Preoperative mechanical ventilation and inotropic support are needed in TA patients with significant respiratory distress due to pulmonary over-circulation or underlying pulmonary disease, as well as in patients with heart failure. Diuretics, afterload-reducing drugs, or inotropes may be needed to reduce pulmonary over-circulation and HF, especially in patients with truncal valve insufficiency. This group of patients is especially at risk of coronary ischemia as diastolic coronary perfusion is compromised by truncal valve regurgitation and discharge into the pulmonary artery. Metabolic and electrolyte disorders, hypoglycemia, and anemia should be corrected to prevent the worsening of heart failure (Vohra et al. 2010; Kang et al. 2021).

Intraoperative Anesthesia Management

TA repair surgery ranks amongst the highest rate of risk for intraoperative cardiac arrest in pediatric patients, either with or without congenital heart diseases, which mandates sophisticated care and extraordinary vigilance to manage the hemodynamic status appropriately (Odegard et al. 2007; Ramamoorthy et al. 2010).

> The main goal in intraoperative anesthesia management is to maintain a delicate balance between the pulmonary blood flow and the systemic blood flow (i.e., Qp/Qs) and to also ensure adequate coronary perfusion

The following considerations should be closely managed to optimize intraoperative anesthesia management of TA patients (Habre et al. 2004; Ziyaeifard et al. 2014; Brenner et al. 2016; Parikh et al. 2018; Du et al. 2019; Johnson et al. 2021):

- The main goal in intraoperative anesthesia management is to create a delicate balance between the pulmonary blood flow and the systemic blood flow (i.e., Qp/Qs) and to also ensure adequate coronary perfusion.
- During and after anesthesia induction, complete invasive monitoring should be established as early as possible, including arterial and central venous catheters, near-infrared spectroscopy, and transesophageal echocardiography.

- Induction of anesthesia is performed with a pinpoint titration of intravenous and/or inhaled anesthetics added with a balanced anesthesia maintenance technique (i.e., volatile anesthetics, narcotics, and muscle relaxants).
- Myocardial ischemia mandates vigilance over any potential myocardial event throughout the intraoperative period.
- Hyperventilation and hyperoxia should also be strictly avoided; otherwise, the preexisting unbalanced pulmonary blood flow may be aggravated in favor of increased pulmonary circulation and at the expense of systemic and coronary circulation.
- If the patient has underlying persistent high pulmonary vascular resistance, any significant drop in systemic vascular resistance reduces pulmonary blood flow and causes hypoxia.
- After sternotomy, increased chest compliance leads to lung expansion which in turn may further reduce pulmonary vascular resistance and accentuate the pulmonary over-circulation.
- Vasopressors and inotropes are recommended but should be used with extreme caution, and if possible, limited to the time of weaning from the CP; the titration of these drugs is required to enhance ventricular contraction and proper balance between afterload and systemic perfusion.
- Vasopressor use is a double-edged sword—it might improve coronary perfusion but at the same time may lead to pulmonary over-circulation due to increased SVR and left-to-right shunting.
- Although inotropes (i.e., ephedrine and epinephrine) increase diastolic blood pressure due to resultant tachycardia, they may also increase myocardial oxygen consumption and exacerbate ischemia.
- Milrinone is widely used to prevent low cardiac output state (LCOS) syndrome after congenital heart surgery. This drug is also useful in TA management because it supports left and right ventricular function and reduces systemic and pulmonary vascular resistance, thus preventing truncal valve insufficiency and pH.
- In postoperative vasoplegia, systemic vasopressors (i.e., vasopressin and norepinephrine) or inotropic drugs with vasopressor properties (i.e., epinephrine and dopamine) are indicated.
- Prophylactic use of inhaled nitric oxide is recommended in these patients especially if valveless conduit grafts are used; mainly due to the high risk of acute pulmonary vasoreactivity, progression of pulmonary hypertension, and the post-repair chance of right ventricular failure.
- An epicardial pacemaker must be available for any probable atrioventricular block as any reconstructive surgery on the interventricular septum, and.
- Similar to other neonatal congenital heart disease surgeries, blood products such as platelets and cryoprecipitate are often needed in TA patients; though their judicious use should not be forgotten.
- Patients with 22q11deletion syndrome should receive more transfusion support in the perioperative period, including irradiated blood products mainly due to the risk of acquired transfusion-induced graft vs. host disease (GVHD).
- For patients with 22q11deletion syndrome, careful attention to blood calcium levels is also a prerequisite, especially if they have received citrated blood products.

Operative Technique in Truncus Arteriosus

General Principles

Truncus arteriosus surgery is one of the most challenging congenital heart operations and close attention to detail with a focus on precision is required. The main goals of surgical repair are separation of systemic and pulmonary circulation, closure of the ventricular septal defect (VSD), establishing a right ventricle (RA) to pulmonary artery (PA) pathway and correction of any associated cardiac lesions (Rodefeld and Hanley 2002; Luo et al. 2018; Alamri et al. 2020; Gellis et al. 2020; Hamzah et al. 2020; Naimo et al. 2020; Padalino et al. 2020).

After usual preparations, the chest is opened via median sternotomy. The pericardium is

opened in the right paramedian line and a pericardial patch is harvested to keep for later usage. The presence of thymic tissue is noticed and partial thymectomy is performed for better exposure of truncus and pulmonary arteries. The absence of the thymus gland may be a part of a chromosomal anomaly that is associated with immunodeficiency and hypocalcemia (DiGeorge Syndrome). Afterward, the external anatomy of cardiac structures, great vessels, and coronary arteries is assessed. The aorta and pulmonary arteries are well dissected and mobilized to facilitate later anastomoses. Both right and left pulmonary arteries are encircled with vascular loops or tapes.

Cannulation and Conduct of Cardiopulmonary Bypass (CPB)

After systemic heparin infusion, the ascending aorta is cannulated as far distally as possible. Bicaval cannulation is performed through the right atrium. CPB is initiated, and the pulmonary arteries are snared to prevent a large systemic flow run off to the pulmonary bed. If there is severe truncal regurgitation, left ventricular distention may occur at the beginning of CPB, so aortic cross-clamping and left ventricular venting should be done expeditiously.

Myocardial protection is very important in such a complicated and long operation. The aorta is clamped as distally as possible, the left heart is vented via a right upper pulmonary vein, cold cardioplegic solution (del Nido or Custodiol solutions) is administrated in the truncal root, and local cooling is provided by ice slash. If the truncal valve is regurgitant, the aorta should be opened and the cardioplegic solution is delivered directly to the coronary Ostia.

Separation of Pulmonary Arteries

According to the anatomic type, pulmonary arteries are separated from the main trunk. After careful inspection of the location and course of coronary arteries, excision of the right and left pulmonary arteries, en bloc or separated, with a cuff of the truncal wall is accomplished. The defect is primarily closed or repaired with a piece of the synthetic patch. If the truncal valve repair is needed, the main trunk is completely transected, from which the confluence of pulmonary arteries is excised. In this manner, distortion of the aortic root after repair of the defect is avoided.

VSD Closure

VSD is usually nonrestrictive and subtruncal in location. Sometimes, it extends inferiorly to become perimembranous. A longitudinal infundibular incision, just beneath the truncal valve, provides the best exposure of VSD. If there is an inferior muscular rim, separating VSD from the tricuspid valve, sutures can be safely placed all around the borders of VSD. In the case of the perimembranous type, posteroinferior sutures should be placed with caution to avoid the conduction system. Dimensions of the VSD patch should at least be equal to the truncal annulus. In the case of restrictive VSD, it can be enlarged by resection of the anterior border.

Reconstruction of RV to PA Pathway

There are two methods for creating a pathway from the right ventricle to the pulmonary artery. The first is by using a valved conduit. Aortic or pulmonic homograft, which is selected and prepared in advance, now is cut in the appropriate length. Distal anastomosis of homograft and pulmonary bifurcation is done with 6-0 or 7-0 sutures. Great care should be paid when performing this anastomosis because control of the suture-line bleeding is very difficult at the end of the operation. Proximal anastomosis of homograft to the right ventricular incision is completed by an autologous pericardial hood. Bovine jugular valved conduit (Contegra) is an acceptable alternative, with almost the same results.

In the second method, as first described by Barbero-Marcial, the surgeon works with the

autologous tissue. After VSD closure, a flap of the truncal wall is turned inferiorly to become the posterior wall of the right ventricle to the pulmonary artery pathway. The left atrial auricle or just the epicardium of the pulmonary artery can also play the same role. Then a sizable pericardial patch, with or without an underneath monocusp valve, makes the anterior wall of the pathway.

Truncal Valve Repair

One of the most important associated lesions is truncal valve regurgitation. Anomalies of the number and configuration of leaflets cause the valve to be regurgitant. If the regurgitation is severe, it should be repaired. The truncal root is transected just superior to the sinotubular junction. Different techniques such as plication, commissuroplasty, or bicuspidization are utilized to make the valve competent. Plication of the truncal wall above the commissures is also helpful to maintain normal valve function.

Weaning from CPB

Any associated anomaly should be addressed during rewarming. The patent foramen ovale is usually left open when operating in the neonatal or early infancy period. Insertion of monitoring catheters (i.e., left atrial or pulmonary artery catheters) makes the process of weaning more precise and uneventful. Some surgeons keep the pulmonary artery catheter for at least 48 h postoperatively to diagnose and/or manage pulmonary hypertension crisis. There is a substantial risk of bleeding due to multiple suture lines, so all of them should be double-checked before weaning from cardiopulmonary bypass. Epinephrine or dopamine plus milrinone is a reasonable inotropic combination that is routinely utilized. As there is a risk of pulmonary hypertension crisis, as well as tamponade or low output state, some surgeons prefer to leave the sternum open for 2–3 days, especially in neonates and small infants.

Risk Factors

Several risk factors have been mentioned in previous studies as outcome determinants of truncal repair; though not complete, the following is a brief list of the proposed risk factors (Ebert et al. 1984; Brown et al. 2001; Tlaskal et al. 2010; Chen et al. 2016; Alamri et al. 2020):

- Coexisting interrupted aortic arch (IAA) (after TA repair),
- Preoperative truncal valve regurgitation,
- Moderate to severe truncal valve regurgitation (after repair),
- Surgery before 1997,
- Prolonged cross-clamping,
- Associated anomalies and coexisting anatomic features,
- Preoperative, perioperative, and postoperative management,
- Preoperative truncal valve regurgitation,
- Associated cardiac anomalies.

Postoperative Care

To maintain acceptable cardiopulmonary outcome in the postoperative period, most patients require a period of hemodynamic support, mechanical ventilation, and sedation with a special focus on the following basic elements of the TA patients:

- Management of pulmonary vascular resistance,
- Adequate systemic perfusion,
- Optimal coronary blood flow.

Fluid and electrolyte management, sedation, pain control, respiratory control, cardiovascular management, renal function, neurological status, infection control, and nutritional status are all important factors to consider during the postoperative period. While noninvasive monitoring of the heart rate, respiratory rate, and oxygen saturation are the most basic requirements, invasive pulmonary and atrial catheters with central and arterial catheters can be used for closer continuous monitoring.

Meanwhile, close vigilance should be maintained towards identifying possible low cardiac output thereby mandating rapid, vigorous management. Using nitric oxide should be continued until the inflammatory response caused by CPB disappears, and the pulmonary vascular resistance moves toward the normal range. Adequate sedation and normocapnia minimize the increase in pulmonary vascular resistance and improve cardiac output. In unstable neonates, keeping the sternum open throughout the first postoperative day(s) could ameliorate hemodynamic stability; however, risks and benefits should be weighed and adjusted (Bosman 2012; Parikh et al. 2018).

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Right-Sided Obstructive Lesions

Robert Wong and Lorraine N. Lubin

Abstract

Tetralogy of Fallot (TOF) is one of the most common cyanotic cardiac defects, accounting for about 3–5% of all congenital cardiac disease, with an estimated incidence of 0.2–0.8 per 100 live births (Apitz et al., Lancet, 374:1462–1471, 2009). Niels Stensen first described it in 1671 with its physiology refined later by Etienne-Louis Fallot in 1888. In 1924, Maude Abbott coined the term tetralogy of Fallot based on the four classic lesions that make up the disease.

Keywords

Tricuspid valve · Ventricular septal defect
Pulmonary valve · Pulmonary blood flow
Right ventricular outflow tract

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Tetralogy of Fallot

Introduction

Tetralogy of Fallot (TOF) is one of the most common cyanotic cardiac defects, accounting for about 3–5% of all congenital cardiac disease, with an estimated incidence of 0.2–0.8 per 100 live births (Apitz et al. 2009). Niels Stensen first described it in 1671 with its physiology refined later by Etienne-Louis Fallot in 1888. In 1924, Maude Abbott coined the term tetralogy of Fallot based on the four classic lesions that make up the disease

1. Ventricular septal defect (VSD)
2. Right ventricular outflow tract (RVOT) obstruction
3. Overriding aorta
4. Right ventricular hypertrophy (Stensen 1671–1672)

Today we know that TOF is a family of disease with similar intracardiac anatomy that can be highly variable in terms of pulmonary artery, RVOT, and pulmonary valve anatomy. Due to its involvement with pulmonary artery and valve and the RVOT, it is discussed here in brief; a full discussion is presented in chapter "Cardiopulmonary Bypass in Children and Infants," Tetralogy of Fallot.

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TOF is also commonly associated with other cardiac anomalies such as anomalous coronary arteries, right aortic arch, and atrioventricular (AV) valve defects.

Although the exact cause of the disease is still unknown, recent studies have shown certain genetic predisposition to the disease. In one study of patients with TOF, 25% were found to have microdeletion of q11 region in chromosome 22. TOF is also commonly found in patients with 22q11 deletions such as in Di George syndrome and velocardiofacial syndrome. In those without any overt syndromes, the prevalence of deletions has been estimated at 6% (Apitz et al. 2009).

Anatomy

The physiology of TOF is largely dependent on the severity of the right outflow tract obstruction. The ventricular defect found in TOF is usually large with unrestricted flow between the two ventricular chambers. As a result of this, right ventricular pressure is reflective of left ventricular pressure, and blood flow across the septal defect follows the path of least resistance. If the right outflow tract obstruction is higher than the resistance of blood going through the aorta, then blood flow will preferentially shunt right to left resulting in decreased pulmonary blood flow and desaturated blood entering the systemic circulation resulting in cyanosis. If left ventricular pressure is higher than right ventricular pressure, then blood flow will preferentially shunt left to right with saturated blood diverted away from the systemic circulation and into the pulmonary vasculature resulting in decreased cardiac output.

Presentation

Clinical presentation can vary depending on severity of anatomical right outflow tract obstruction and degree of shunting across the septal defect. Newborn with severe right outflow obstruction will present with cyanosis secondary to decreased pulmonary blood flow and increased mixing of desaturated blood. Those with moderate-to-mild right outflow obstruction are usually asymptomatic unless agitated in which cyanosis can ensue. Many with mild obstruction are diagnosed incidentally with auscultation of a harsh systolic murmur on exam. Those with mild obstruction can have pulmonary overcirculation and develop heart failure. Although most TOF are symptomatic and cyanotic to a certain degree, there are some who remain well saturated without any cyanosis for a period of time (PINK TET).

Majority are asymptomatic when comfortable and at rest. However, agitation and crying can worsen the right outflow tract obstruction resulting in cyanosis best seen in the lips and nail beds. As mentioned before a systolic murmur is usually present from the right outflow tract obstruction. Classically, it is described as a crescendo-decrescendo murmur heard best at the left mid-upper sternal border. As RVOT obstruction increases, so does the flow across the septal defect and the turbulent flow through the RVOT and the severity of the murmur. During severe "tet spells" when all blood is diverted across the septal defect, the systolic murmur may become absent.

Physical exam along with electrocardiogram (EKG) and chest X-ray can be used for diagnosis, but echocardiography is used to confirm the disease. EKG will usually demonstrate signs of right axis deviation from increased right ventricular pressure, while chest X-ray may demonstrate the classic boot-shaped heart secondary to right ventricular hypertrophy. Using two-dimensional echocardiography, multiple components of TOF can be evaluated for preparation of surgical correction. The location and number of VSD should be noted. Both the degree of aortic override and extent of the septal defect can be evaluated via the parasternal and apical view. As mentioned before, the degree of right outflow tract obstruction can vary with location and severity and must be delineated prior to surgical correction. The parasternal short axis and subcostal coronal and sagittal views are best used to evaluate the pulmonary valve and right outflow tract. The pulmonary annulus should be assessed to determine if a transannular patch is needed during surgical correction. The pulmonary artery along with its branches should also be evaluated in the paraster-

nal short axis, looking at size and anatomy. The coronary arteries should also be assessed with the parasternal short-axis and long-axis view looking for aberrant anatomy, specifically where the left anterior descending coronary originates from. This is important because anterior crossing coronary vessels may complicate surgical repair of right outflow tract obstruction. The aorta should also be assessed using the parasternal notch short- and long-axis view looking for anatomy and potential aortopulmonary collaterals and a patent ductus arteriosus (PDA). Echocardiography can also be used to assess the degree of outflow tract obstruction by assessing blood flow via color Doppler and gradient calculation using the modified Bernoulli equation.

Treatment

Surgical repair of TOF usually occurs within the first year of life, usually before six months of age. It can be staged if the infant is too small to tolerate cardiopulmonary bypass, and time is needed for the infant to grow or completely repaired shortly after birth. Early repair for appropriate infants is currently the preferred route given the excellent outcomes. Studies have shown that minimizing right ventricular exposure to high pressure prevents irreversible remodeling of the right ventricle, specifically right ventricular hypertrophy and right ventricular failure (Al Habib et al. 2010). Goals of surgical repair are to relive the RVOT obstruction and separate the systemic circulation from the pulmonary circulation by closing off the VSD.

Most full infants undergo complete repair shortly after birth via an intra-atrial or intraventricular approach. Most prefer the intra-atrial approach so as to minimize scarring and injury to the ventricle, which can lead to impaired function and conduction abnormities postoperatively. Using either approach, the surgeon can relieve pulmonary stenosis, resect infundibular and subinfundibular muscle bundles, or create a transannular patch to open up the RVOT obstruction and patch up the VSD (Morales et al. 2009). In addition to minimizing damage to the ventricle, many surgeons attempt to maintain pulmonary valve competency by using a "valve sparring approach" whenever possible. This technique is applied to individuals with adequate pulmonary valve annulus size, as they do not need a transannular patch, unlike individuals with small or borderline annulus who usually require a transannular patch (Airan et al. 2006; Karamlou et al. 2006). Although a transannular patch opens up the RVOT obstruction, it also makes the pulmonary valve incompetent resulting in pulmonary insufficiency.

An alternative surgical approach is to create a valve conduit between the RV and the PA. Valve incompetency, regurgitation, and conduit stenosis are all complications that can occur overtime with a conduit.

Small and premature infants usually require a staged approach to correction due to high mortality associated with going on bypass. As a result they usually undergo a central shunt or BT shunt placed temporarily to provide an adequate source of pulmonary blood flow while they grow to an adequate size to tolerate a complete intracardiac repair on bypass. Once the child is of adequate size, the palliative pulmonary shunt is taken down, and the right outflow tract obstruction opened to allow for adequate pulmonary blood flow. At the same time, the VSD is closed off so to avoid shunting at the ventricular level.

Anesthetic Considerations

Anesthetic management of individuals with TOF should be to promote forward blood flow from the RV to the lungs and limiting right to left shunting of deoxygenated blood through the VSD. As mentioned before, the pathophysiology of TOF is decreased antegrade flow to the lungs secondary to the RVOT obstruction with shunting across the VSD resulting in cyanosis.

Depending on the severity of the obstruction, individuals may require supplemental oxygen therapy. Agitation to the infant should be avoided when possible as crying can increase pulmonary pressures and further decrease pulmonary perfusion and increase the amount of deoxygenated blood shunted systemically

through the VSD. Premedication with oral midazolam (0.5 mg/kg) prior to inhalation induction can minimize the amount of stress and agitation and thus minimize "tet spells" that may result in severe cyanosis. Ketamine (1–4 mg/kg) and fentanyl can be used for induction if intravenous access is available. Adequate ventilation and oxygenation are important in these individuals as hypoxemia and hypercarbia can both increase pulmonary vascular resistance and result in overall increased right-sided pressures and obstruction. Tet spells with severe cyanosis benefit from Neo-Synephrine (5–10 μg/kg) to increase the SVR. The alpha1 agonist results in direct vasoconstriction with increased left ventricle pressures, reversing the right to left shunt through the VSD and limiting deoxygenated blood into the systemic system. Another benefit of Neo-Synephrine is that it has no inotropic effects on the heart, which is beneficial as increased cardiac contractility and tachycardia can further impede pulmonary blood flow if the RVOT obstruction is dynamic such as in infundibular spasm. Increasing the depth of anesthesia with volatile agents can also be used for negative inotropic effects. Although this may help with infundibular spasm, it can also result in vasodilatation and drop in SVR, which can worsen shunting through the VSD. Volume infusion and maintaining adequate preload will help by increasing right heart filling pressure and increase overall blood pressure.

Arterial line should be placed opposite side of planned BT shunt if a stage procedure is being done, as the shunt can cause a steal effect resulting in an artificially lower blood pressure reading. Central line placement should be considered for volume replacement and vasoactive drug infusions post bypass.

Postoperatively, it is not uncommon to see decreased RV function or even RV failure as their RVs have been exposed to high pressures. This, coupled with injury to the ventricles during surgical repair, can result in less than optimal RV function immediately after surgery and may require vasoactive drugs such as epinephrine and milrinone (0.25–05 μg/kg/min) for hemodynamic support. Abnormal conduction is also a common occurrence postoperatively given the close proximity of the conduction pathway to the VSD repair. As a result, atrioventricular pacing capability should be available to maintain AV synchrony, which will help with the RV function and cardiac output.

Congenital Pulmonic Valve Stenosis

Introduction

The incidence of congenital pulmonic stenosis is approximately 0.6–0.8 per 1000 live births and accounts for about 10% of all congenital cardiac disease (Hoffman and Kaplan 2002). Pulmonic stenosis is defined as right ventricular tract obstruction at the level of the pulmonary valve. Where along the pulmonary valve, the obstruction occurs can vary.

Anatomy

Classically, the stenosis is at the valve with fusion of the valvular tissue around a fixed orifice resulting in a dome-shaped deformity. Koretzyk described a subset of pulmonary valve dysplasia where instead of the classic fused valves, the valves are not adherent to each other. Instead, obstruction occurs from (1) thickened leaflets rendering them rigid and immobile and (2) occurrence of tissue in the sinuses that restrict lateral movement of leaflets during systole. It is important to delineate between the two, as pulmonary valve dysplasia is associated with higher failure rates with balloon valvuloplasty compared to pulmonary valve stenosis and is commonly seen in Noonan's syndrome (Koretzky et al. 1969). Less common is subvalvular obstruction from fibromuscular narrowing below the pulmonary valve, which is associated with other congenital cardiac lesions such as TOF. Subvalvular lesions can be dynamic where increased contractility of the ventricle causes increase in obstruction. Supravalvular stenosis can also occur with narrowing of the pulmonary artery above the pulmonary valve.

The underlying cause of pulmonic stenosis is unknown. During the fifth week of gestation, the conotruncus (bulbus cordis) divides into the ascending aorta and the main pulmonary artery. The pulmonary valve develops from the distal conotruncus, moving anterior and leftward of the aortic valve. Some have hypothesized that pulmonary stenosis occurs from maldevelopment of the distal conotruncus.

Presentation

Clinical presentation of congenital pulmonic stenosis can vary depending on the degree of stenosis. Those with trivial to mild pulmonary stenosis (gradient <40) are usually asymptomatic besides having a pulmonary ejection murmur at the second intercostal space. Multiple studies have shown those with mild pulmonic stenosis will usually have no progression of their disease and is generally considered benign (Drossner and Mahle 2008; Rowland et al. 1997).

Moderate pulmonary valve stenosis (gradient between 40 and 60) can present with poor weight gain secondary to dyspnea and fatigue with feeding. Disease progression is somewhat variable with studies showing RVOT obstruction, decreased cardiac output, and increased right ventricular end-diastolic pressures later on in life (Hayes et al. 1993).

Those with severe stenosis (gradient >60) at birth can present with cyanosis from atrial shunting, heart failure from increased right ventricular end-diastolic pressure, and right ventricular hypertrophy and can lead to irreversible right ventricular dysfunction if not treated promptly (Krabill et al. 1985; Johnson 1962; Stone et al. 1974).

Critical pulmonic stenosis is the most severe with inadequate pulmonary blood flow through the RVOT. Because of this, it is paramount that the ductus arteriosus remains patent for pulmonary blood flow. Presentation is similar to severe pulmonic stenosis and if not treated in a timely manner it may become life threatening (Freed et al. 1973).

Depending on the severity of the stenosis, patients may have enlarged right atrium and right ventricular hypertrophy manifesting radiographically as an enlarged cardiac silhouette and with right axis deviation on EKG.

Echocardiography is recommended to confirm the diagnosis of pulmonic stenosis given the relative ease at which the pulmonary valve and right heart can be visualized through transthoracic echocardiogram. Besides visualizing the amount of blood flow across the pulmonic valve, continuous wave Doppler can be used to estimate the gradient across the valve. A transvalvular gradient of <40 mmHg is considered mild stenosis, 40–60 mmHg moderate stenosis, and >60 mmHg severe stenosis.

Treatment

Balloon valvuloplasty is the first-line treatment for pulmonic stenosis confined to the valvular level. Those with critical pulmonic stenosis may require balloon valvuloplasty shortly after birth, whereas those with mild-to-moderate stenosis may have the valvuloplasty done electively at a later date with observation first. Balloon valvuloplasty is done through percutaneous access via the femoral vein, where a wire is advanced through the pulmonary valve. Once in position, a balloon is placed through the pulmonic valve and inflated to dilate the stenotic valve. It is not uncommon to see pulmonary regurgitation post balloon therapy. The amount of regurgitation can be limited by optimizing balloon size (Rao 2007). Right ventricular enlargement can develop overtime from the regurgitant flow. Currently, there is no consensus regarding the timing of pulmonary valve replacement in those with severe pulmonary regurgitation post balloon valvuloplasty.

Those with typical pulmonic stenosis have excellent outcomes with balloon valvuloplasty with majority having gradients less than 20 mmHg post intervention. Potential complications with balloon valvuloplasty include perforation of the pulmonary valve, right ventricle, pulmonary artery, and damage to tricuspid valve

(TV) resulting in regurgitant flow (Rao 2007; Stanger et al. 1990). Balloon valvuloplasty can also be used to treat dysplastic pulmonary valves, although outcomes are less favorable when compared to dome-shaped pulmonic stenosis and surgical correction may be required (Stanger et al. 1990; Tabatabaei et al. 1996).

Surgical repair is usually needed for dysplastic, supravalvular, and subvalvular pulmonary stenosis. With dysplastic pulmonary valve, surgical excision of the thickened leaflets and sometimes a transannular patch are needed to relive the obstructive lesion. Surgical correction is also recommended for supravalvular lesions due to the close proximity to the pulmonary artery, and most will require a transannular patch. Subvalvular lesions usually have a muscular component to the obstruction making balloon valvuloplasty an ineffective treatment option.

Anesthetic Considerations

The anesthetic goal for individuals with pulmonic stenosis is to promote forward blood flow from the RV to the pulmonary artery and to ensure adequate pulmonary perfusion. Individuals with severe stenosis and cyanosis may require supplemental oxygenation and prostaglandin therapy to ensure adequate oxygenation. For surgical repairs, arterial line should be placed for close blood pressure monitoring. Central access should be obtained for volume replacement and vasoactive drug infusion. Depending on the severity of the disease and preexisting RV function, inotropic support may be needed immediately after the surgical repair. Those with severe pulmonic stenosis may have dysfunctional RV and require inotropic agents such as milrinone (0.25–0.5 μg/kg/min) and dobutamine (1–5 μg/kg/min) to maintain cardiac output. Inotropic support should be used cautiously for individuals with subvalvular stenosis, as there is usually a dynamic component to the stenosis and the increased contractility and tachycardia can worsen the obstruction. Volume infusion and adequate preload can help with RV filling pressure and promote forward flow from the RV. However, careful titration of volume should be considered for those with borderline RV function as too much preload can add additional stress to the ventricle and result in worsening function and decrease cardiac output. Adequate ventilation strategy is also important as hypercarbia and hypoxemia can both increase PVR and add additional strain to the already dysfunctional RV.

Pulmonary Atresia with Intact Ventricular Septum

Introduction

In pulmonary atresia with intact ventricular septum (PA/IVS), there is atresia of the pulmonary valve resulting in absent connection between the right ventricular outflow tract and the pulmonary artery. In addition, there is no communication between the two ventricles because of the intact septum and thus no way of mixing, making this a fatal structural cardiac defect unless surgically corrected.

PA/IVS accounts for approximately 3% of all congenital cardiac defects with an estimated incidence of 4 to 8 per 100,000 live births (Hanley et al. 1993; Ekman Joelsson et al. 2001; Ashburn et al. 2004). Unlike pulmonary atresia with VSD, the cause of the PA/IVS is currently not known. There does not appear to be any associated genetic syndrome associated with the defect. There are hypotheses that it is an acquired defect in utero secondary to viral or inflammatory disease-causing pulmonary valve atresia and abnormal fetal blood flow ultimately leading to PA/IVS (Kutsche and Van Mierop 1983).

Because of the wide range of anatomical defects found in PA/IVS, there is now a uniform reporting system defining PA/IVS as a congenital malformation with right ventricular outflow obstruction that is ductal dependent and can include pulmonary atresia, variable degree of tricuspid and right ventricular hypoplasia, and aberrant coronary anatomy (Lacour-Gayet 2000).

Anatomy

The pulmonary atresia in PA/IVS can be either muscular or membranous with majority being membranous. In membranous pulmonary atresia, the pulmonary valve annulus is small with fused leaflets resulting in RVOT obstruction. The right ventricle and infundibulum are usually well formed in membranous pulmonary atresia. Muscular pulmonary atresia occurs in about 25% of PA/IVS and is associated with poor outcome secondary-to-severe right ventricular hypoplasia and anomalous coronary arteries (Dyamenahalli et al. 2004; Daubeney et al. 2002; Kipps et al. 2011). In muscular pulmonary atresia, the muscular infundibulum is obliterated resulting in complete obstruction of the RVOT.

The anatomy of the right ventricle in PA/IVS can vary widely from a dilated thin-walled ventricle to a severely hypoplastic hypertrophied ventricle. Normally the RV is divided into three parts or tripartite, the (1) inlet, (2) body, and (3) outlet. Those with a tripartite RV will allow for a biventricular repair, whereas bipartite or unipartite, with absent body and/or outlet, will need univentricular repair due to the inability to support full pulmonary blood flow (Dyamenahalli et al. 2004; Daubeney et al. 2002).

The tricuspid valve (TV) can also vary from small to dysplastic with stenotic or regurgitant flow. The size of the tricuspid valve has been found to correlate with the anatomy of the RV. A TV with a Z score of -4 will usually have a unipartite RV making biventricular repair unlikely, whereas a TV Z score of -2 to 0 is associated with a tripartite ventricle, making biventricular repair possible (Ashburn et al. 2004).

Coronary anatomy can also vary in PA/IVS from absent aortocoronary connection to stenosis and abnormal left to right coronary connections. Normally coronary perfusion is dependent on diastolic pressure and diastolic flow. However, in PA/IVS, fistulae can form between the RV and coronary arteries. This combined with absent aortocoronary connections makes coronary perfusion dependent on retrograde flow from the RV during systole or right ventricle-dependent coronary circulation (RVDCC). Recognition of RVDCC is important to note as these patients are dependent on elevated RV pressures providing coronary perfusion via the fistulae between the RV and coronaries, and relieving the RVOT obstruction will decompress the right ventricle resulting in inadequate coronary perfusion, ischemia, infarction, and sudden cardiac death (Calder et al. 2007; Giglia et al. 1992). Because of this, it is important to delineate the anatomy of the RV, TV, and coronary circulation, as all three play a role in determining if the child will have a biventricular, 1½, or univentricular surgical repair.

Unlike PA/VSD, PA/IVS usually has normal anatomy distal to the pulmonary valve. Majority will have normal confluent branches coming off the main pulmonary artery with a left ductus supplying pulmonary blood flow. In some there are abnormal pulmonary artery with arterial connections between the aorta and pulmonary artery called major aortopulmonary collaterals (MAPCA).

In PA/IVS, there is RVOT obstruction from the pulmonary atresia and no blood flow from the RVOT to the pulmonary artery. Instead pulmonary blood flow depends on regurgitant flow into the right atrium where it can cross over to the left atrium via a patent foramen ovale and supply blood to the lungs via the ductus arteriosus. Because of this, all newborns with PA/IVS must have a patent ductus arteriosus in order to survive, as that is the only means of pulmonary blood flow. Those with PA/IVS will usually have a smaller PDA compared to normal infants due to decreased pulmonary blood flow through the ductus in utero. RV pressures in these patients are determined by the extent of RV egress. Those with severe tricuspid regurgitation may have normal RV pressures as blood flows freely back into the right atrium and is shunted to the left atrium via the patent foramen ovale. However, in those with limited tricuspid regurgitation, RV pressure can become suprasystemic as the blood cannot move forward or backward. If RV sinusoids exist, blood can flow through these channels into the systemic circulation via the coronary circulation.

Presentation

Infants with PA/IVS will usually present with cyanosis secondary to right to left shunting at the atrial level and complete RVOT obstruction. Most neonates with PA/IVS will have normal fetal and birth history with tachypnea and hyperpnea during the newborn period. However, if untreated, PA/IVS is ultimately fatal with approximately 50% dying within two weeks and 85% dying within six months (Leonard et al. 2000). As mentioned before, those with PA/IVS are dependent on a PDA for pulmonary blood supply and survival. Closure of the ductus arteriosus will lead to rapid deterioration including acidosis, hypoxia, cardiogenic shock, and ultimately death. There have been rare reports of PA/IVS surviving on aortopulmonary collaterals once the ductus arteritis closes off (McArthur et al. 1971). Depending on the anatomy, a variety of murmurs can be appreciated on auscultation. Those with severe tricuspid regurgitation will have a systolic murmur, while a continuous murmur might be heard secondary to the PDA. Similarly, chest X-ray in those with PA/IVS can be normal or have an enlarged cardiac silhouette if they have severe tricuspid regurgitation resulting in enlarged right atrium and ventricle. EKG will usually show left axis deviation secondary to absent or hypoplastic RV.

PA/IVS can be diagnosed via fetal ultrasound starting at the second trimester. Using the four-chamber view, one can look for an atretic pulmonary valve and hypoplastic tricuspid valve and right ventricle. Evaluating the anatomy of flow across the PDA can also help with diagnosing PA/IVS. In normal fetus, flow across the PDA is usually pulmonary to the aorta with the ductus in a horizontal position. However, in PA/IVS the ductus is usually vertically oriented with flow across the PDA reversed, from aorta to pulmonary given the lack of communication between the RVOT and pulmonary artery (Sandor et al. 2002; Emmel et al. 2004).

Postnatally, diagnosis of PA/IVS is usually done with echocardiographic imaging and pulse wave Doppler showing atretic pulmonary valve and absent pulmonary blood flow. It is important to differentiate between PA/IVS and critical pulmonic stenosis as both can have similar findings echocardiographically. Besides diagnosis of PA/IVS, echocardiography can be used to evaluate the anatomy of these patients, which can vary widely as mentioned before. Right ventricle function and size should be measured as well as tricuspid annulus size as both play a role in determining the kind of surgical repair. Intracardiac mixing should also be assessed across the foramen ovale and ductus arteriosus to determine adequate pulmonary blood flow. Although angiography is the gold standard, as much of the coronary circulation and anatomy should be delineated by echocardiography to determine any aberrant coronary circulation and the possibility of sinusoids or fistulae between the RV and coronary circulation.

Cardiac catheterization is key in delineating coronary anatomy and circulation in PA/IVS. As mentioned before, PA/IVS is associated with an abnormal coronary circulation, from stenotic coronary vessels, anomalous or absent aorto-coronary origins, and sinusoids and fistulae between the RV and coronary circulation. With cardiac catheterization, contrast is injected at the aorta to visualize the presence or absence of aortocoronary vessels and their individual intracardiac course. Contrast can also be injected into the RV to look for any communications between the RV and coronary circulation. It is essential to rule out RVDCC as decompression of the RV in these patients can lead to coronary steal, ischemia, infarction, and even death. In addition to the coronary anatomy, angiography can also be used to determine TV and RV size and morphology.

Treatment

Initial treatment of newborn with PA/IVS should be stabilization, ensuring adequate cardiopulmonary support. As pulmonary flow is supplied solely by the PDA, prostaglandin infusion is usually initiated to keep the PDA open. Supplemental oxygen and mechanical ventilation should be considered if there is marked cyanosis, hypoxia,

or increased work of breathing. Inotropic support may also be needed for those with hypoperfusion and increasing metabolic acidosis. The amount of shunting across the atrial septum may also be inadequate due to a small PFO which will result in decreased cardiac output where by balloon atrial septostomy can be performed to increase mixing and the cardiac output. Almost all newborn with PA/IVS will have adequate shunting across the PFO as those with small or absent atrial communication usually undergo fetal demise.

There is currently no uniform approach to surgical repair in neonates with PA/IVS given the wide variety of anatomical difference found in the disease.

After initial stabilization, the focus should be on assessing the anatomy of the individual, including RV and TV size and coronary anatomy so as to decide on the appropriate surgical repair. Currently the surgical options include biventricular repair, palliative univentricular, or 1½ ventricular repair. Rarely cardiac transplantation is required when none of the three repairs are feasible. In biventricular repair, the pulmonary and system circulation are separated with two pumping ventricles providing blood flow to each. This usually requires a well-formed right ventricle and tricuspid valve without RVDCC to support adequate pulmonary blood flow. Univentricular repair is a palliative procedure where the pulmonary and systemic circulation is separated but with only one ventricle. The univentricular approach is reserved for those with small or hypoplastic RV that cannot provide adequate support for pulmonary blood flow. In the 1½ ventricle repair, the pulmonary and system circulation are separated with the left ventricle acting as the systemic pump and the right ventricle acting as the pulmonary pump partially. The 1½ ventricle repair is usually done when the RV or TV size is borderline and there is uncertainty regarding the RV's ability to support the entire pulmonary blood flow. As a result, a Glenn procedure is done where the RV only has to support half the pulmonary blood flow, whereas the other half from the SVC flows passively into the pulmonary artery. The benefit of this approach is that it preserves a two pumping ventricle system, and as the right ventricle is rehabilitated with improved size and function, it may eventually be able to support the entire pulmonary circulation. Cardiac transplantation is usually reserved for PA/IVS with aorto-coronary atresia as they have extremely high mortality rates even with palliative repairs (Odim et al. 2006).

Anesthetic Considerations

Anesthetic goals and management for PA/IVS vary depending on the anatomy of the disease and the planned repair. Arterial line should be placed for close blood pressure monitoring and central access obtained for vasoactive drug infusion and volume replacement. Management of those undergoing a palliative shunt rests on balancing the pulmonary circulation with the systemic circulation. Ventilation should be aimed toward normocarbia and adequate oxygenation as hyperventilation can cause overcirculation of the pulmonary vasculature resulting in hypotension from a steal phenomenon from the systemic circulation.

Individuals undergoing a biventricular repair have hypertensive RV and can have RV dysfunction after surgical repair of the pulmonary atresia. Pulmonary hypertension is not uncommon postoperatively from the sudden increase in pulmonary blood flow to an unadjusted pulmonary vascular bed. Inotropic support along with adequate filling pressures is important in these patients in order to promote forward blood flow and to prevent collapse of the RV. Using nitric oxide to decrease the PVR and off-load the strained RV postoperatively can be beneficial in these patients. Mechanical ventilation strategy should be aimed toward lowering PVR and maintaining adequate oxygenation. Pulmonary edema from the acute increase in pulmonary flow postoperatively is also common and can cause difficulties in oxygenation. Because of this, care should be taken when considering early extubation for these patients even though mechanical positive ventilation can increase PVR and work against the dysfunctional RV.

Anesthetic goals of individuals undergoing the 1½ ventricle repair rest on adequate passive pulmonary blood flow and supporting forward blood flow from a partially unloaded RV. Maintaining adequate preload helps with passive pulmonary perfusion along with RV filling pressures for cardiac output. Ventilation strategy to prevent hypercarbia and hypoxemia should be employed to avoid increase in PVR and to promote passive pulmonary blood flow. Inotropic support may be needed to support RV dysfunction and the work of breathing. Early extubation if possible is preferred, as positive pressure mechanical ventilation increases intrathoracic pressure and can impede pulmonary blood flow.

Pulmonary Atresia with VSD

Introduction

Pulmonary atresia with VSD (PA/VSD) is a relatively rare congenital disease and is secondary to pulmonary atresia with a VSD and major aortopulmonary collateral arteries (MAPCA) supplying the pulmonary circulation. There is an estimated incidence of about 0.7 per 10,000 live births with approximately one-fifth of all TOF being PA/VSD variant (Malformations of the cardiac outflow tract in genetic and environmental risk factors of major cardiovascular malformations 1981). Just like TOF, there appears to be a genetic component to the disease with 22q11.2 deletion and 1q21.1 deletion both associated with PA/VSD (Carotti et al. 2010; van Engelen et al. 2010; Silversides et al. 2012).

Anatomy

Like TOF, PA/VSD consists of an anteriorly maligned ventral septal defect and overriding aorta, but instead of varying degree of RVOT obstruction, the pulmonary valve is atretic with complete obstruction of the RVOT. Like PA/IVS, the atretic pulmonary valve can be at the valvular level (membranous) or occur at the subpulmonary infundibulum (muscular). Because of the atretic pulmonary valve, there is no antegrade pulmonary blood flow from the RVOT during fetal growth, resulting in abnormal development of structures distal to the pulmonary valve such as small or atretic pulmonary artery and its branches. If a ductus arteriosus is present, pulmonary blood flow can originate from the ductus, resulting in confluent pulmonary arteries of varying size. If there is no ductus arteriosus, MAPCAs develop and provide pulmonary blood supply. MAPCAs originate from the splanchnic plexus in utero and eventually form tortuous connections between the aorta and various branches of the pulmonary artery (Liao et al. 1985). The number and size of the MAPCAs can vary with areas of stenosis commonly found more distally. The arborization patterns of the MAPCA are also variable and many times incomplete, leaving certain lung segments overperfused and others underperfused and becoming more narrow overtime. It is important to delineate the pulmonary artery anatomy and presence of MAPCAs in PA/VSD as they play an important role in determining management of the disease.

Presentation

Clinical presentation in those with PA/VSD can vary depending on the degree of intracardiac shunting and amount of pulmonary flow to the lungs. Those with a PDA will usually have some degree of cyanosis as most will lack any MAPCAs and are dependent on the PDA for pulmonary blood. These individuals require prostaglandins to keep their ductus open before their surgical treatment. Those without a ductus arteriosus will develop MAPCAs and depending on the amount of flow through the MAPCAs may be cyanotic or normally saturated. Those with small or restrictive MAPCAs will have insufficient pulmonary blood flow and present with cyanosis, whereas those with large and unrestricted MAPCAs will have normal saturations, but also overcirculation of the pulmonary vascular bed and left ventricle and over time developing pulmonary hypertension and heart failure.

PA/VSD can be diagnosed during the second trimester via fetal ultrasound, looking for pulmonary atresia in utero (Seale et al. 2009). Postnatally,

the diagnosis of PA/VSD is confirmed with echocardiography. EKG is usually unremarkable with normal sinus rhythm with right axis deviation from right ventricular hypertrophy. Chest X-ray will show the characteristic boot-shaped heart from RV hypertrophy with hypoperfused lung fields if MAPCAs are restrictive or pulmonary edema if MAPCAs are unrestrictive. Echocardiography will show the typical anterior maligned VSD with an overriding aorta along with pulmonary atresia with no blood flow from the RV to the pulmonary artery. Presence of MAPCAs should also be sought out via continuous blood flow patterns. Because echocardiography will not be able to delineate all MAPCAs, cardiac catheterization and angiography are needed to investigate the entire pulmonary vasculature anatomy along with all supplying MAPCAs. MRA and CT angiography can be used to look at the pulmonary vasculature anatomy, but because it does not provide hemodynamic information and has less refined imaging, they are not routinely utilized (Lin et al. 2012).

With cardiac catheterization, diagnostic angiography can be used to look at all sources of pulmonary blood flow along with detailed images of the native pulmonary artery anatomy. In addition to identifying all MAPCAs supplying the pulmonary vasculature, it is important to note what lung segments are supplied by MAPCAs and/or native pulmonary artery and if any of the vessels are restrictive or stenotic. Furthermore, hemodynamic information can be obtained such as pressures and areas of stenosis in each MAPCA, along with pressures in the pulmonary vasculature. All of this information is important in an individual in PA/VSD when deciding how to surgically repair the disease.

Treatment

Initial treatment in neonates with PA/VSD should be to stabilize the patient ensuring adequate cardiopulmonary support. Given the complexity and spectrum of the disease, initial treatment can vary. For those with cyanosis, therapy should be aimed at increasing pulmonary blood flow. If a PDA exists, prostaglandin should be initiated to keep the ductus open to maintain pulmonary circulation. Supplemental oxygen may be needed if the ductus or MAPCAs are too restrictive and not providing adequate pulmonary blood flow resulting in marked cyanosis.

Those with pulmonary overcirculation from unrestricted MAPCAs will have normal oxygen saturations but will also have signs of pulmonary congestion and can lead to heart failure. Mechanical ventilation should be considered for those with pulmonary edema as they can tire out easily from the increased work of breathing. Diuretic therapy should be started to off-load the heart and treat the pulmonary edema.

After the patient is stabilized, the surgical correction can be planned. As mentioned above, PA/VSD can present with a spectrum of pulmonary artery anatomy and MAPCAs. Because of this, the surgical approach can vary depending on the individual's anatomy, but the goals are always to (1) relieve the RVOT obstruction so that adequate blood flow can occur between the RV and the lungs, (2) ensure that the pulmonary arteries are of adequate size either through reconstruction or rehabilitation of the vessels, (3) reattach the collaterals from the aorta to the pulmonary arteries (unifocalization), and (4) close the VSD.

Surgical repair should aim to lower RV pressures as studies have shown PA/VSD with elevated RV pressure postoperatively are associated with higher mortality (Kirklin et al. 1983). To achieve this, any RVOT obstruction is relived so that there is no impedance of flow from the RV to the PA. Total cross-sectional area of the pulmonary vasculature is maximized by recruiting as many lung segments as possible and correcting any stenotic vessels. It is also important to promote as much antegrade pulmonary blood flow so as to allow for continued growth of the hypoplastic pulmonary arteries.

In the best-case scenario where an individual has large collaterals with normal-caliber pulmonary vessels, a single-stage repair can be done where collaterals are unifocalized, the RVOT obstruction corrected, and the VSD closed off.

Unifocalization can be done as a staged approach if the pulmonary arteries are too small or if there are multiple segmental stenoses. For

these individuals, a central shunt between the aorta and the hypoplastic pulmonary artery is created without unifocalization of the collaterals, to allow for maximal pulmonary artery growth. After three to six months, a cardiac catheterization is done to evaluate the growth and caliber of the pulmonary arteries to see if unifocalization is possible. If there is adequate pulmonary artery growth with low pulmonary pressures, unifocalization of the collaterals can occur with relief of the RVOT obstruction and repair of the VSD. The risks of undergoing unifocalization early on in life with small pulmonary arteries are thrombosed vessels, development of stenosis, and lack of collateral vessel growth (Liava'a et al. 2012; Fouilloux et al. 2012; D'udekem et al. 2005; Duncan et al. 2003). Individuals with small-caliber pulmonary arteries without severe segmental level stenosis can undergo collateral unifocalization in a single approach. Again a central shunt is created to promote pulmonary artery growth and development followed by collateral reanastomosis from the aorta to the native pulmonary arteries. However, the VSD and RVOT are left uncorrected until a later time when there is evidence that there is sufficient pulmonary artery growth and an adequate pulmonary vascular bed for the RV to supply the entire pulmonary blood flow. If the VSD is closed prior to creation of an adequate pulmonary vascular bed, RV dysfunction may ensue from increased pulmonary afterload, and without the VSD acting as a pop-off valve, it can lead to RV failure. Another option is to close the VSD, and if it appears that the RV cannot support the full pulmonary perfusion, a fenestration can be made at the VSD repair to offload the RV. Once it is evident that the RV can support the full pulmonary circulation, the fenestration can be closed via transcatheter approach.

Anesthetic Considerations

As mentioned before, PA/VSD is essentially an extreme form of TOF, and thus anesthetic management is similar. Adequate ventilation should be used to decrease PVR and promote pulmonary perfusion. Major blood loss should be anticipated secondary to multiple suture lines from unifocalization of MAPCAs. Central access or large bore intravenous access should be available to replace volume loss along with arterial line for close hemodynamic monitoring.

RV dysfunction is not uncommon post CPB secondary to increased afterload from inadequate pulmonary vascular bed. Strategies to decrease PVR should be employed such as adequate ventilation and nitric oxide therapy, while inotropic support with milrinone, dobutamine, and epinephrine is used for inotropic support RV function. Patients with PA/VSD are not candidates for early extubation as unifocalization can result in lung reperfusion injury resulting in pulmonary edema, making ventilation and oxygenation difficult. Intrapulmonary bleeding from multiple vascular suture lines can also impede adequate ventilation. Frequent bronchial suctioning should be used with the support of PEEP to maintain adequate ventilation. Aggressive pain control should also be implemented to minimize systemic and pulmonary hypertension, which can cause bleeding from the multiple vascular suture line.

Ebstein's Anomaly

Introduction

Ebstein's anomaly is a rare congenital defect of the tricuspid valve and the right ventricle, with varying anatomic morphology. It accounts for less than 1% of all congenital heart disease with an estimated incidence of 1 in 200,000 live births, affecting males and females equally (Lupo et al. 2011; Correa-Villaseñor et al. 1994). Studies have shown a heterogeneous genetic predisposition to the disease, while other studies have shown a correlation between lithium intake during pregnancy and Epstein's anomaly (Allan et al. 1982; Attenhofer Jost et al. 2007).

Anatomy

The tricuspid valve divides the right atrium from the right ventricle and normally consists of three leaflets (anterior, septal, and posterior) that are

attached to the tricuspid valve annulus. In Ebstein's anomaly, the tricuspid leaflets are malformed secondary to failure to split during embryological development, with one or more leaflets attached to the right ventricle endocardium. The anterior leaflet is the largest of the three leaflets and usually remains attached to the tricuspid annulus, while the septal and posterior leaflets are usually absent or fused if present, with abnormal attachment to the right ventricle endocardium. This results in a dilated annulus with posterior downward displacement of the leaflets toward the RVOT creating a funnel-shaped tricuspid valve that is incompetent with varying degrees of regurgitation. In Ebstein's anomaly, the right ventricle is also divided into two chambers due to the abnormal attachment of the tricuspid valve onto the right ventricle endocardium. The proximal RV is known as the atrialized chamber due to apical displacement of the leaflets resulting in a continuous communication with the right atrium, while the distal chamber is the actual ventricle consisting of the trabecular and outlet portion of the RV.

Ebstein's anomaly is classified based on Carpentier's classification of the tricuspid valve, which provides important information about whether the tricuspid valve can be repaired or needs to be replaced. In type A, the true RV volume is adequate; type B, the anterior leaflet of the tricuspid valve moves freely with a large atrialized portion of the RV; type C, the anterior leaflet movement is severely restricted with possible RVOT obstruction; and type D, almost complete atrialization of the RV with some infundibulum present (Dearani and Danielson 2000). Another classification system is through echocardiographic description of the disease as mild, moderate, or severe, with descriptions of the amount of displacement of the valves and the degree of RV dilation (Allan et al. 1982). This method is not as descriptive and precise as Carpentier's classification but is much more simple.

Ebstein's anomaly has a high association with other cardiac defects such as bicuspid or atretic aortic valves, pulmonary atresia or hypoplastic pulmonary artery, subaortic stenosis, coarctation, mitral valve prolapse, accessory mitral valve tissue or muscle bands of the left ventricle, VSDs, and pulmonary stenosis.

Pathophysiology of Ebstein's anomaly is regurgitation of the blood flow through the tricuspid valve from the abnormal leaflets and functional impairment of the RV secondary to the partially atrialized RV. With the increased regurgitant flow and atrialized RV, the right atrium becomes enlarged overtime causing further increase in a dilatation of the tricuspid valve annulus. With worsening regurgitant flow, the RV goes into failure, increasing right-sided pressures and resulting in interatrial shunt and cyanosis.

Presentation

Clinical presentation and symptoms can vary from asymptomatic-to-severe cyanosis and RV failure depending on the anatomic severity and age of onset of the disease and other coexisting cardiac defects. Newborns with severe forms of Ebstein's anomaly can present with cyanosis, cardiomegaly, and heart failure. Those with mild regurgitation and limited atrialization of the RV can present without any symptoms as a newborn and remain asymptomatic until late teens or well into adulthood. Once symptomatic, these individuals can have arrhythmias from the dilated right atrium and fatigue and cyanosis from the increased regurgitant flow and failing RV. Although rare, there have been cases of anatomical defect so severe that cardiomegaly, hydrops, and heart failure occur in utero leading to death.

Physical exam will vary depending on severity of disease. Newborns with severe forms of Ebstein's anomaly will present with severe cyanosis from increased right atrial pressures and interatrial shunting and signs of heart failure such as cardiomegaly and enlarged liver. Those with mild disease are usually asymptomatic and may present with only a systolic murmur with mid-diastolic murmur from the increased regurgitant flow across the tricuspid valve. Despite the severe regurgitant flow, V waves are often missing in jugular venous pulse secondary to the large right atrium absorbing the increased back-

flow volume. Chest X-ray can show a globular silhouette with normal or decreased pulmonary vascularity. EKG is usually abnormal in Ebstein's anomaly with most displaying a tall P wave from the enlarged right atrium along with a right bundle branch block. Ebstein's anomaly is also associated with AV conduction and arrhythmias secondary to AV node compression and abnormal central fibrous body formation. Although complete heart block is rare, it is estimated that up to 42% can present with first-degree AV block (Attenjofer et al. 2005).

Diagnosis is usually with echocardiography, using the four-chamber view to evaluate the degree of apical displacement of the tricuspid valve along with the function of the right ventricle and any other intracardiac defects that might be present. The apical displacement of the septal leaflets of the tricuspid valve should be at least 8 mm/m^2 body surface area from the attachment of the anterior leaflet of the mitral valve. The individual tricuspid leaflets should be evaluated, looking for signs of failure of delamination and accessory attachments. The size of both the right atrium and right ventricle should be measured. The degree and location of the regurgitant flow and size of the annulus should be assessed for feasibility of a tricuspid valve repair versus replacement.

Treatment

Treatment of individuals with Ebstein's anomaly depends on the severity of the anatomical defect and its associated symptoms. Many with mild disease are asymptomatic and only require frequent follow-up with a cardiologist. Prostaglandin therapy should be started on newborns with severe cyanosis in order to maintain pulmonary perfusion via the ductus arteriosus. Nitric oxide may also be helpful in decreasing pulmonary pressures and promoting forward flow from the RV to the pulmonary vascular bed. Signs of heart failure should be treated with diuretics and digoxin. Individuals with Ebstein's anomaly are at high risk for thromboembolism, especially older patients with atrial fibrillation or unrepaired atrial shunts. It is recommended that these individuals undergo anticoagulation therapy (Warnes et al. 2008).

Surgical repair of Ebstein's anomaly should be delayed as long as possible due to the high mortality associated with surgical repair in the newborn period (Knott-Craig et al. 2007; Starnes et al. 1991). Surgery should be considered in adults with paradoxical emboli, signs of cyanosis, or signs of deteriorations from worsening heart failure such as cardiomegaly, decreased ventricular function, or progressive right ventricular dilatation. Presence of premature ventricular contractions or atrial tachyarrhythmia are also indications for surgical correction as they can be early indicators of increased stress on the right ventricle and are associated with higher surgical mortality (Attenjofer et al. 2005).

Surgical repair of Ebstein's anomaly in the neonate can vary depending on the severity of the anatomy and associated intracardiac defect. Biventricular repair is done when there is good delamination of the anterior valve with good mobility and adequate RV size and function. Single ventricle repair is reserved for those with a severely dysplastic anterior leaflet with small RV and pulmonary artery atresia. Those with good delamination of the anterior leaflet but with poor RV function or dilated RV can undergo 1½ ventricle repair where a bidirectional cavalpulmonary shunt is created to decrease the systemic venous volume load on the RV. Whenever appropriate, valve repair is preferred over replacement given lower complications and mortality (Augustin et al. 1997; Vargas et al. 1998). Although there does not appear to be any difference in rate of reoperation with bioprosthetic valve versus mechanical valve, most will replace with a bioprosthetic valve given the high incidence of thrombosis with mechanical valve and the need for lifetime anticoagulation therapy with mechanical valve. The valve is usually placed in an interatrial position with possible complications including coronary compression and injury to the conduction tissue resulting in complete AV conduction block.

Anesthetic Considerations

Given the wide spectrum in presentation of Ebstein's anomaly, all individuals should have a complete assessment of the severity of their disease including symptoms such as exercise tolerance and presence of cyanosis. Those with cyanosis may require prostaglandin therapy to keep their PDA open for adequate pulmonary circulation. Individuals with Ebstein's will also benefit from decreased pulmonary vascular resistance. Nitric oxide can be used to lower PVR to promote pulmonary blood flow, along with adequate ventilation strategies to prevent hypercarbia and hypoxemia. Ketamine (1–4 mg/kg) or etomidate (0.2–0.3 mg/kg) can be used for intravenous induction. Those without intravenous access can be induced via a smooth inhalation induction with oral versed (0.5 mg/kg) for anxiolysis to minimize agitation as crying can increase PVR and worsen cyanosis. Arterial line should be placed for close blood pressure monitoring. If undergoing a single ventricle repair, the arterial line should be placed opposite side of the planned shunt placement. Central access should also be considered for vasoactive drug infusions and volume replacement both intraoperatively and postoperatively. Given the high risk for embolic events, all lines should be cleared of air bubbles, and filters should be placed in all intravenous lines. Depending on the severity of the disease, individuals may benefit from inotropic support postoperatively with milrinone (0.25–0.5 μg/kg/min) or dobutamine (1–5 μg/kg/min), especially those with preexisting RV dysfunction. Adequate preload may also help hemodynamically in those with poor functioning RV. Nitric oxide can also be beneficial in off-loading the right ventricle if dysfunction is present postoperatively. Dysrhythmias such as supraventricular tachycardia, functional rhythm, and AV block are common postoperatively given the proximity of the repair to the intracardiac conduction pathway, and temporary pacing wires should be considered.

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Congenital Mitral Valve Anomalies

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Abstract

Congenital anomalies of the mitral valve represent a broad spectrum of lesions that are often associated with other congenital heart anomalies. The reported incidence of congenital anomalies of the mitral valve in an echocardiographic study of 13,400 subjects was 0.5% (Banerjee et al., Am J Cardiol 76:1284–1291, 1995). These lesions affect valve function in a variable manner. When indicated, surgical intervention results in good long-term results (Hoashi et al., Ann Thorac Surg 90:36–41, 2010; Lee et al., Eur J Cardiothorac Surg 37:267–272, 2010; Serraf et al., Circulation 102: III166–III171, 2000). In the last few years, enhanced knowledge of the functional as well as anatomical aspects of these lesions accompanied by concomitant significant advances in the diagnosis as well as anesthetic and surgical management has contributed to improved outcomes. This chapter provides an overview of the different congenital malformations that can affect the mitral valve excluding mitral valve anomalies in atrioventricular septal defects (AVSD) and univentricular hearts and focuses on the anesthetic and surgical management of these congenital mitral anomalies.

Keywords

Mitral valve · Left atrium · Mitral regurgitation · Papillary muscle · Mitral valve repair

Introduction

Congenital anomalies of the mitral valve represent a broad spectrum of lesions that are often associated with other congenital heart anomalies. The reported incidence of congenital anomalies of the mitral valve in an echocardiographic study of 13,400 subjects was 0.5% (Banerjee et al. 1995). These lesions affect valve function in a variable manner. When indicated, surgical intervention results in good long-term results (Hoashi et al. 2010; Lee et al. 2010; Serraf et al. 2000). In the last few years, enhanced knowledge of the functional as well as anatomical aspects of these lesions accompanied by concomitant significant advances in the diagnosis as well as anesthetic and surgical management has contributed to improved outcomes. This chapter provides an overview of the different congenital malformations that can affect the mitral valve excluding mitral valve anomalies in atrioventricular septal defects (AVSD) and univentricular hearts and focuses on the anesthetic and surgical management of these congenital mitral anomalies.

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Embryology

The embryology of the mitral valve is complex and its knowledge is crucial for understanding the various anomalies that can affect it. Mitral valve formation begins during the fourth week of gestation. During the sixth week, fusion of the endocardial cushions partitions the atrioventricular canal into right and left atrioventricular junctions (Kanani et al. 2005). Failure of fusion of the superior and inferior cushions, presumably secondary to a deficiency of the vestibular spine, is responsible for producing atrioventricular septal defects. Normally, the lateral cushion forms the posterior mitral leaflet, while the anterior leaflet derives from the union of the left part of the superior and inferior cushions. During the eighth week, the shape of the mitral orifice looks like a crescent, the two ends of which are connected to compacting columns in the trabecular muscle of the left ventricle (LV). These columns form a muscular ridge, the anterior and posterior parts of which become the papillary muscles (Oosthoek et al. 1998). The metamorphosis of the ridge into the papillary muscles implies a gradual loosening of muscle, which is called delamination. The abnormal compaction of the ventricular trabecular myocardium is responsible for producing mitral valve prolapse. Simultaneously, as for the tricuspid valve, the cushion tissue loses contact with the myocardium of the ridge, except at the insertion of the future tendinous cords. The very rare Ebstein's malformation of the mitral valve results from a failure of excavation of the posterior leaflet from the parietal ventricular wall. The chordae can be demarcated between the 11th and 13th week of development by the appearance of defects in the cushion tissue at the place where the tips of the papillary muscles are attached to the leaflets. Both leaflets and chordae originate from the cushion tissue as verified by their similar immunohistochemical characteristics (Oosthoek et al. 1998). In contrast, papillary muscles are derived from the ventricular myocardium. A lack of evolution of the tendinous cords results in hammock or arcade mitral valve. The more severe anomaly of the leaflet is represented by the imperforate mitral valve. Finally, as each stage of this embryological development may be abnormal, the different malformations of the mitral valve can be either isolated or associated.

Classification of Congenital Mitral Valve Anomalies

The published literature to date reports seven classification systems of congenital mitral valve lesions (in the setting of concordant atrioventricular and ventricle–atrial connections with the exclusion of atrioventricular canal defects and hypoplastic left heart syndrome) that are outlined in Table 1.

Anatomical Classification Systems

Davachi and colleagues, in 1971, were one of the first to systematically assess and classify congenitally malformed mitral valves based on postmortem assessment (Davachi et al. 1971). They used a segmental classification according to whether the lesion affected the leaflets, commissures, tendinous chords, or papillary muscle arrangements. In 1977, Collins-Nakai et al. critiqued this segmental classification as they noted 97% (37 out of 38) of their patients with congenital mitral stenosis had more than one segment of the mitral valve apparatus affected (Collins-Nakai et al. 1977). They concluded that it was misleading to classify patients based on one anatomic segment of the mitral valve (Collins-Nakai et al. 1977). They proposed a classification based on associated cardiac defects (e.g., associated left-sided lesion, tetralogy of Fallot, or no associated defects) (Table 1).

In 1978, Ruckman and van Praagh focused their attention on stenotic mitral valve defects and noted that typically congenital mitral stenosis affected multiple valve segments (Ruckman and van Praagh 1978). Commonly, the leaflet margins were thickened, tendinous chords appeared shortened, interchordal spaces were obliterated, and the two papillary muscles were underdeveloped and closely spaced. They coined the term "typical congenital mitral valve stenosis" to describe this most

Table 1 Classification systems of congenital mitral valve anomalies

Author	Year	Basis of classification	MV lesions	Classification system
Davachi et al. (1971)	1971	Anatomical	MS and MR	Segmental classification of MR and (surgical + autopsy)
				MS based on predominant lesion:
				1. Leaflet
				2. Commissures
				3. Chords
				4. Papillary muscles
Carpentier et al. (1976)	1976	Surgical	MS and MR	Classification based on predominant
Chauvaud et al. (1998)	1998[a]	Surgical	MR only	Lesion:
				MR:
				Type 1: normal leaflet motion
				Type 2: leaflet prolapsed
				Type 3: restricted leaflet motion
				(a) normal papillary muscle
				(b) abnormal papillary muscle
				MS:
				(a) predominant valvular lesion with normal papillary muscle
				(b) predominant valvular lesion with abnormal papillary muscle
Collins-Nakai et al. (1977)	1977	Anatomical	MS only	Based on associated lesions: (surgical + autopsy + echo)
				1. Isolated MV disease
				2. Supramitral ring ± other cardiac defects
				3. MS and other left-sided lesions or atrial shunt
				4. MS and tetralogy of Fallot
Ruckman and van Praagh (1978)	1978	Autopsy	MS only	1. Typical congenital MS
				2. Hypoplastic congenital MS
				3. Parachute mitral valve
				4. Supramitral ring
				5. Double orifice mitral valve
Moore et al. (1994)	1994	Echo + surgical	MS only	1. Typical hypoplastic MV symmetrical papillary muscles
				2. Atypical hypoplastic MV—asymmetrical papillary muscles
				3. Parachute mitral valve
				4. Supramitral ring
				5. Double orifice mitral valve
Mitruka and Lamberti (2000)[b]	2000	Descriptive	MR and MS	1. Hemodynamic: MR, MS, or mixed
				2. Segmental:
				(a) Supravalvular
				(b) Valvar (1) and annular (2) leaflet
				(c) Subvalvular (1) and chordal (2) papillary muscle
				(d) Mixed

(continued)

Table 1 (continued)

Author	Year	Basis of classification	MV lesions	Classification system
Oppido et al. (2008)	2008	Surgical	MR and MS	1. Hemodynamic:
				(a) Predominant MR
				(b) Predominant MS
				2. Functional:
				(a) Normal leaflet motion
				(b) Prolapsed leaflet
				(c) Restricted leaflet
				3. Segmental:
				(a) Annulus/leaflets
				(b) Chords
				(c) Papillary muscles
				(d) Mixed
				4. Leaflet tissue:
				(1) Dysplastic
				(2) Non-dysplastic

MR mitral regurgitation, *MS* mitral stenosis, *MV* mitral valve
[a] Revised in 1998
[b] Congenital heart surgery nomenclature and database project

common defect with two distinct papillary muscle arrangements. The remainder of stenotic mitral valve defects were classified as "parachute mitral valve" (a single papillary muscle variant), "hypoplastic mitral valve" (miniature valve as seen in hypoplastic left heart syndrome), "double orifice mitral valve," and "supramitral ring." "Supramitral ring" earned a category of its own even though from their work it was clear that it was rarely an isolated defect. As a result, by necessity, some patients were classified into multiple categories based on this system. In 1994, Moore et al. (1994) expanded van Praagh's classification by adding "atypical congenital mitral stenosis" to differentiate between groups with symmetrical (typical mitral stenosis) and asymmetrical (atypical mitral stenosis) papillary muscle arrangements. His description of "atypical congenital mitral stenosis" resembled Oosthoek's (Oosthoek et al. 1997) description of "parachute-like asymmetrical valve" (see complex mitral valve lesions).

Surgical Classification

In 1976, Carpentier et al. (1976) introduced a surgical classification system to specifically facilitate the development of tailored techniques for congenital mitral valve repair. It was based on the "predominant lesion," as he also observed that multisegment pathology was the most prevalent. His description and classification were based on observations at surgery made via the left atrium. Prior to this all classifications were based on the pathologists' view of the defect. The Carpentier classification was based on leaflet motion: normal, restricted, or prolapsed. In addition, it considered the predominant anatomic and hemodynamic effects (Table 1). This description of congenital mitral valve defects was widely accepted and utilized over the next three decades (Serraf et al. 2000; Carpentier et al. 1976; Chauvaud et al. 1998; Oppido et al. 2008; Uva et al. 1995; McCarthy et al. 1996; Prifti et al. 2002; Stellin et al. 2010; Wood et al. 2005; Zias et al. 1998). His team dramatically expanded the repertoire of operative techniques and in doing so popularized mitral valve repair for congenital defects. In 2008, Oppido and colleagues (2008) further refined the classification system by adding a further level to Carpentier's classification, the quality of leaflet tissue: normal or dysplastic. In their surgical series, dysplastic leaflets were associated with less favorable and less durable repairs.

Complex Congenital MV Lesions

Anatomical pathologists and cardiac surgeons introduced descriptive terms for what they perceived as very distinct congenital mitral valve lesions. However, many have argued that the majority of cases do not fit the classic morphologic pattern but are the incomplete forms or the so-called forme fruste (Rosenquist 1974; Mitruka and Lamberti 2000). As a result, these descriptive terms are not stand-alone terms and require further clarification to facilitate effective communication.

"Parachute mitral valve" refers to an anomaly of the mitral valve apparatus where all tendinous cords insert into one papillary muscle as noted by Edwards in 1963 (Schiebler et al. 1961). The other papillary muscle is either absent or severely hypoplastic. As a pathologist, he observed the mitral valve through the incised left ventricle and noted that the anomaly had a parachute-like appearance. Others later observed that in the setting of isolated papillary muscle, the tendinous chords are often short and fused with interchordal spaces partially or completely obliterated (Hoashi et al. 2010; Davachi et al. 1971; Chauvaud et al. 1998; Shone et al. 1963). Commissures are frequently underdeveloped and the leaflets may be dysplastic or deficient. The combination of these lesions can give rise to a funnel rather than a parachute-like appearance. It is frequently associated with a "supramitral ring" (Davachi et al. 1971; Ruckman and van Praagh 1978) that is often an integral part of the mitral valve leaflets (Banerjee et al. 1995; Asante-Korang et al. 2006). It is a membranous or fibrous shelf that arises from the atrial side of the anterior mitral valve leaflet and posteriorly attaches to the leaflet, annulus, or the left atrial wall below the level of the left atrial appendage (Banerjee et al. 1995). Parachute mitral valve is commonly classified as a malformation of the papillary muscles. However, that is too simplistic. It is often the associated lesions of other valve segments (e.g., commissural underdevelopment, dysplastic leaflets, and shortened and fused tendinous chords) that determine the severity of valvar dysfunction (stenosis and regurgitation) and hence the need for cardiac intervention.

In addition to a supramitral ring, parachute mitral valves are frequently associated with subaortic obstruction and coarctation of the aorta. When obstruction at all four levels is present, it is then referred to as Shone's complex (Shone et al. 1963).

Parachute-like asymmetrical valve was described by Oosthoek et al. (1997) in 1997 as an anomaly that is an incomplete form of the true parachute valve with two papillary muscles: one hypoplastic and the other dominant receiving the majority of tendinous chords. He further described that one of the papillary muscles was often elongated, located higher in the left ventricle with its tip reaching to the annulus, and attached at both its base and lateral side to the left ventricular wall. The valve leaflets could be directly attached to the hypoplastic papillary muscle. Parachute-like asymmetrical valves formed a spectrum of anomalies, rather than a well-defined entity. Only one out of Oosthoek's 29 cases could be described as a "true" parachute valve (Oosthoek et al. 1997). Two decades earlier Rosenquist also demonstrated that most papillary muscle anomalies were often mild or incomplete forms (which were common among patients with coarctation) and that the "true" parachute anomaly, with a single papillary muscle, was rare (Rosenquist 1974).

Anomalous mitral arcade was first described by Layman and Edwards in 1967 as "an anomaly of the mitral valve that consisted of connection of the left ventricular papillary muscles to the anterior mitral valve leaflet, either directly or through the interposition of unusually short tendinous chords" (Layman and Edwards 1967). When viewed from the left ventricle, the two papillary muscles resembled two pillars, and the bridging fibrous tissue in-between the papillary muscles resembles the arch of an arcade.

Hammock mitral valve was first described in 1976 by Carpentier et al. (1976), and it referred specifically to the appearance of the mitral valve apparatus from its left atrial aspect as viewed at cardiac surgery. The hammock appearance arose when the valvar orifice was at least partially obstructed by intermixed tendinous chords that attached to abnormal papillary muscles implanted just beneath the posterior leaflet (Carpentier and Brizard 2006).

Double orifice mitral valve is a rare anomaly (0.05% of congenital cardiac abnormalities) that is usually found incidentally or in combination with other abnormalities, most commonly AV canal defects. In itself, it is rarely a cause of significant regurgitation or stenosis (Zalzstein et al. 2004).

Although it is not a true mitral valve lesion, it is convenient to include cor triatriatum (heart with three atria) in the discussion. It is rare—0.5% of congenital cardiac defects—and may be associated with other defects including atrial septal defect (ASD) (see below), anomalous pulmonary venous drainage, VSD, bicuspid aortic valve, coarctation of the aorta, Fallot's tetralogy, double outlet right ventricle (DORV), common AV canal, persistent left superior vena cava (SVC) with unroofed coronary sinus, and hypoplastic mitral valve.

Both right (very rare) and left atrial forms occur, but the left atrial type, or *cor triatriatum sinister*, is of concern here. A membrane dividing the left atrium into an upper and a lower chamber exists, and its presentation is similar to that of mitral stenosis, though if the orifice is large enough, it may be asymptomatic, and only discovered incidentally or in later years when it fibroses or calcifies or when investigating the onset of atrial fibrillation. The membrane lies above the level of the left atrial appendage, whereas a mitral ring lies below it. In its simplest form (20% of cases), there is a membrane with a single or multiple (10%) orifices in it. The majority of the remainder (about 70%) are associated with an ASD, either above the membrane or below it, with the direction of the shunt through the ASD being determined by the relevant pressure gradients at the time, usually left to right in the former (e.g., though right to left if associated with Fallot's tetralogy) and right to left in the latter.

Clinical Features

The nature and severity of symptoms in patients with congenital mitral valve anomalies relate to etiology, rate of onset and progression, left ventricle function, pulmonary artery pressure, and the presence of coexisting valvular or myocardial diseases.

Congenital Mitral Stenosis

Patients with severe mitral stenosis may present with respiratory distress from pulmonary edema shortly after birth if a significant atrial septal communication is not present. The presence of an atrial septal defect decompresses the left atrium, resulting in a clinical picture of pulmonary over circulation and decreased systemic cardiac output.

Patients with mild-to-moderate mitral stenosis present after the neonatal period with signs of low cardiac output and right heart failure such as pulmonary infections, failure to gain weight, exhaustion and diaphoresis with feeding, tachypnea, and chronic cough.

Children with mitral stenosis may present with the insidious onset of exercise limitation and other clinical signs.

Pulmonary congestion is evidenced by increasing severity of dyspnea (depending on the degree of mitral stenosis) that may range from dyspnea during exercise to paroxysmal nocturnal dyspnea, orthopnea, or even frank pulmonary edema. Dyspnea may be precipitated or worsened by an increase in blood flow across the stenotic mitral valve (e.g., pregnancy, exercise) or by a reduction in diastolic filling time achieved by increasing the heart rate (e.g., emotional stress, fever, respiratory infection, atrial fibrillation with rapid ventricular rate).

Signs of right heart failure, including peripheral edema and fatigue, may be present.

Patients with mitral stenosis, including those previously without symptoms, may develop atrial fibrillation, although this is an uncommon event in childhood. It results from chronic distension of the left atrium. Atrial fibrillation may cause loss of the atrial kick to left ventricle filling that reduces systemic output; this may precipitate or exacerbate congestive heart failure. Thromboembolic events (seeding of systemic emboli) occur in 10–20% of patients with mitral stenosis. Many of these emboli lodge in the brain, causing a stroke. Infective endocarditis (a rare event) should be suspected when embolization occurs during sinus rhythm.

Hemoptysis may be caused by rupture of dilated bronchial veins. Pink frothy sputum may be a manifestation of frank pulmonary edema.

Both are associated with end-stage severe mitral stenosis but rarely occur in pediatric patients.

Chest pain occurs in approximately 15% of patients with mitral stenosis.

Dysphagia can be produced by compression of the esophagus as a result of a dilated left atrium. It rarely occurs in children.

Hoarseness can occur if the dilated left atrium impinges on the recurrent laryngeal nerve. It is a rare manifestation of severe mitral stenosis, especially in childhood.

Congenital Mitral Regurgitation

Children with minor degrees of mitral regurgitation are usually asymptomatic. With increased amounts of mitral regurgitation, fatigue may be reported, but children can tolerate severe mitral regurgitation surprisingly better than adults can. Once pulmonary hypertension develops, complaints such as tachypnea and dyspnea with light activity become more prominent. With the most severe mitral regurgitation, children may experience limited growth and failure to thrive. Hemoptysis can develop during the later stages. Children may remain asymptomatic with no complications of mitral regurgitation until the second or third decade of life. An indolent course of mitral regurgitation may be deceptive because of the ability of the heart to compensate for the altered hemodynamics. This occurs because of changes in cardiac pump loading such that increased diastolic filling increases preload, whereas left ventricular ejection, in part into the left atrium, reduces afterload. By the time symptoms become apparent, serious and irreversible LV dysfunction may have developed.

Vital signs are usually normal in mild regurgitation. With increasing mitral regurgitation, heart and respiratory rates may be increased. In patients with severe mitral regurgitation, arterial pulse has been characterized as having a small volume with a sharp upstroke. Rarely, irregular pulse may be indicative of associated atrial fibrillation.

A left atrial lift is a second impulse resulting from the increased volume that is displaced into the left atrium during systole. The second impulse should be felt near the time of the second heart sound. This sign is most helpful in thin children and young adults because their chest diameters are smaller and their hearts are closer to the chest wall. The cardiac impulse may be displaced to the left, and, in more advanced disease, a double impulse is felt.

Upon auscultation, the first heart sound is usually slightly diminished, whereas the second heart sound is usually split. With more severe mitral regurgitation, a third heart sound and a mid-diastolic low-frequency murmur may be present, caused by increased ventricular filling. When pulmonary hypertension develops, the pulmonary component of the second heart sound becomes louder and occurs earlier (as long as right ventricular function is not significantly impaired), reducing the splitting interval. Ejection systolic click may be present due to mitral valve prolapse.

Patients with mild mitral regurgitation may reveal no signs other than a characteristic apical systolic murmur. The mitral regurgitation murmur is characterized as blowing and high pitched, and it is loudest over the apex with radiation to the left axilla. The murmur is often pansystolic, beginning immediately after the first heart sound, and may continue beyond the aortic component of the second heart sound, thus obscuring the second heart sound. This murmur increases with increased afterload (squatting) and decreases with decreased preload (standing). Occasionally, radiation toward the sternum occurs when posterior leaflet abnormalities are present. Little correlation is noted between intensity of the murmur and severity of mitral regurgitation. The murmur occasionally may be confined to late systole only. The degree of mitral regurgitation in these patients is usually mild.

Congestive heart failure with pulmonary edema can occur with significant mitral regurgitation and pulmonary findings may be consistent with it. Compression of left main bronchus due to left atrial enlargement can cause ipsilateral wheezing and lung collapse. Significant and sustained mitral regurgitation can be associated with endocarditis and thromboembolism and have associated findings.

Diagnosis

The diagnosis of congenital mitral valve anomaly relies on the clinical findings, the chest radiography, the electrocardiogram (ECG), and most importantly the echocardiographic assessment. The positive diagnosis can often be made before the echocardiographic evaluation in the presence of an isolated mitral valve anomaly.

Congenital Mitral Stenosis

Electrocardiography

Electrocardiography findings may be normal in patients with mild mitral stenosis. Hemodynamically significant stenosis results in ECG findings of left atrial or biatrial enlargement and right ventricular enlargement in proportion to the severity of the obstruction.

Chest Radiography

Chest radiographic findings may include left atrial dilation, posteroanterior dilation secondary to high pulmonary vascular pressure and resistance, pulmonary venous congestion, and right ventricular enlargement.

Echocardiography

Echocardiography is the most important diagnostic tool to evaluate patients with mitral stenosis. This noninvasive imaging modality provides excellent anatomic and hemodynamic assessment of mitral stenosis.

Echocardiography provides the following:

- Direct anatomic data, such as visualization of valve leaflet morphology and motility as well as measurement of valve orifice dimensions
- Evaluation of left atrial size and detection of left atrial thrombi
- Indirect physiologic data (i.e., estimation of pressure gradients across the mitral valve and right ventricular systolic pressure), which may be measured using Doppler echocardiography.

Transesophageal Echocardiography

Transesophageal echocardiography (TEE) is used when transthoracic echocardiographic pictures are inadequate. It may also be used to guide intervention and assess results in the operating room and cardiac catheterization laboratory.

Dynamic Three-Dimensional (3D) Transthoracic and Transesophageal Echocardiography

These techniques can provide good insight into valvular motion and help preoperative planning in situations in which valve reconstruction is considered (Kutty et al. 2014). However, the accuracy of these techniques is currently limited by the quality of the original two-dimensional (2D) echocardiographic cross-sectional images, which can be adversely affected by patient motion, breathing, and cardiac arrhythmia such as atrial fibrillation.

Congenital Mitral Regurgitation

Chest Radiography

With mild mitral regurgitation, the heart size is normal. With increasing mitral regurgitation, cardiomegaly may develop, and left atrial enlargement becomes apparent. Left ventricle enlargement and pulmonary congestion may also be present. In cases of acute mitral regurgitation, pulmonary venous vascular markings may be increased and pulmonary edema may be seen without signs of left atrial enlargement. Left lung atelectasis and hyperinflation may be visible due to compression of the left main bronchus by enlarged left atrium.

Electrocardiography

The 12-lead ECG is likely to show normal results in children with mild mitral regurgitation. In more chronic mitral regurgitation, ECG findings demonstrate left atrial and left ventricle enlargement. When pulmonary hypertension is present, ECG may also demonstrate right ventricular

hypertrophy. Rhythm changes, such as atrial fibrillation, are often observed in adults but are rare in children.

Transthoracic Echocardiography

Echocardiography is the most valuable technique used to evaluate mitral regurgitation. Echocardiography is usually readily available and portable. Knowledge of mitral valve apparatus, including the labeling of the scallops of each of the two valve leaflets, is essential. An understanding of the anatomy from surgeon's perspective is needed to explain the findings.

Two-dimensional (2D) echocardiography allows depiction of the size of the chambers and assessment of ventricular systolic function, as well as determination of the morphology of the mitral valve leaflets, the annulus, chordal tissue, and papillary muscles. The parasternal long axis view may provide the best images of mitral valve prolapse, whereas the parasternal short axis view is better for depicting papillary muscle anatomy and leaflet cleft.

M-Mode assessment of cardiac function is extremely important. Cardiac function should be carefully evaluated in mitral regurgitation, and one can use different techniques, including 2D, three-dimensional (3D), tissue Doppler, and strain imaging to assess the left ventricle function. The left ventricular ejection fraction should be hypernormal, indicating a preserved myocardial function with mitral regurgitation. In the presence of normal or mildly depressed function, one should expect myocardial failure postoperatively. Scalloping of mitral leaflets can occur in mitral valve prolapse and can be seen using M-Mode. In addition, ventricular dimensions should be measured and followed for left ventricle enlargement. Left ventricular hypertrophy can also be determined and may be present in hypertrophic cardiomyopathy with mitral regurgitation.

Color-flow Doppler echocardiography demonstrates width and direction of the regurgitant flow (Little et al. 2008). The degree of regurgitation may be underestimated if the jet hugs the walls of the atrium. Furthermore, because the structures are 3D, multiple views and scans must be performed with optimal transducer frequency and gain to determine the entire regurgitant jet.

Spectral Doppler imaging demonstrates a high-velocity signal across the mitral valve in systole entering retrograde into the left atrium. Mitral regurgitation can be seen and evaluated best in the apical four-chamber and parasternal long views. Concomitant mitral stenosis should also be determined. The peak velocity of mitral regurgitation can be used to calculate several other parameters, including left ventricle dP/dT.

Visualizing mitral regurgitation is not as difficult as classifying the severity. In adults, many echocardiographic methods are used with varying results. The grading of mitral regurgitation in the pediatric population as mild, moderate, and severe is based on the size and extent of the color-flow Doppler signal (jet area) into the left atrium (left atrial area).

Other factors to consider include left atrium and ventricular size and function. In mild mitral regurgitation, the signal is located in the proximal third of the left atrium near the mitral valve. The left atrium is usually not enlarged, and the ventricular function is normal. In moderate mitral regurgitation, the signal extends to the mid cavity, with left atrial dilation and increased ventricular function. With severe mitral regurgitation, the signal reaches the posterior third of the left atrium and the pulmonary veins, and the left atrium and ventricle are usually enlarged, with increased ventricular shortening fraction. Other techniques useful in quantification include measurement of vena contracta, proximal isovelocity surface area, systolic pulmonary vein flow reversal, and regurgitant fraction.

Transesophageal Echocardiography (TEE)

This may be required if further detailed anatomic information is needed. Transesophageal echocardiography views correlate better with angiographic grading than transthoracic views. In addition, intraoperative transesophageal echocardiography is absolutely essential in guiding mitral valve surgery and assessing the result.

3D Echocardiography

This provides an excellent anatomical evaluation of mitral valve and helps with decisions regarding therapy and possible surgical intervention.

Cardiac Magnetic Resonance Imaging

Cardiac magnetic resonance imaging (MRI) is a newer modality. Cardiac MRI provides 3D imaging of the heart and great vessels and does not depend on acoustic windows, as echocardiography does. Cardiac MRI provides more accurate evaluation of both left and right ventricular size and function. The degree of mitral regurgitation determined by cardiac MRI has not been adequately evaluated. However, velocity flow imaging may potentially provide additional information.

Cardiac Catheterization

Evaluation of mitral regurgitation in children usually does not require cardiac catheterization. Some pediatric patients undergo catheterization to evaluate other cardiac defects that may be present, or anomalous left coronary from the pulmonary artery (ALCAPA) is suspected, as this can cause mitral regurgitation secondary to myocardial ischemia or infarction.

Mitral regurgitation is best evaluated using angiography obtained in the right anterior oblique view. Retrograde flow of injected dye demonstrates the degree of mitral regurgitation, which is quantitatively graded (grades I–IV) depending on the level of left atrial opacification (Table 2). Left ventricular injections obtained via the retrograde approach are preferred to an anterograde approach to prevent the catheter from holding the mitral valve open and creating artifactual mitral regurgitation.

To quantitate mitral regurgitation, a combination of angiography and cardiac output measurements must be used. Either thermodilution or the Fick principle helps measure forward cardiac output, while angiography allows determination of total left ventricular output. Keep in mind that tricuspid regurgitation can invalidate the thermodilution method (Calafiore et al. 2009).

Subtracting the forward output from total left ventricular output yields the regurgitant fraction. A regurgitant fraction of 0.5 or greater is generally considered clinically significant.

The left ventricular ejection fraction may be increased initially; however, as the left ventricle decompensates, the ejection fraction decreases to normal or subnormal values, signifying left ventricular failure. As left ventricular failure develops, left ventricular end-diastolic pressure increases, resulting in an increase in left atrial and pulmonary venous pressure. Increased pulmonary venous pressure is manifested as an increase in pulmonary capillary wedge pressure. At catheterization, the wedge pressure *a* wave amplitude is increased along with a rapid rise of the *v* wave. The latter occurs when left ventricular compliance decreases.

Cardiac catheterization should be used when noninvasive data are discordant, limited, or differ from the clinical status of the patient. Ventriculography may add new information if more complex congenital cardiac problems are present.

Table 2 Estimation of mitral regurgitation using angiography

Regurgitation grade	Description
Grade of 1+	Trace amounts of contrast are seen in the left atrium, but the amount is insufficient to outline the left atrium
Grade of 2+	The contrast opacifies the entire left atrium but less than that of the LV. The contrast clears quickly (within 2–3 beats)
Grade of 3+	The contrast opacifies the left atrium and LV equally
Grade of 4+	The contrast opacifies the left atrium more than the LV and progresses to the pulmonary veins

LV left ventricle

Management of Congenital Mitral Valve Anomalies

In the past decade, the surgical approach to congenital mitral valve disease has significantly evolved as successive midterm and long-term series have been reported (Serraf et al. 2000; Chauvaud et al. 1998; Oppido et al. 2008; Uva et al. 1995; Prifti et al. 2002). Pediatric patients can derive the same benefits from mitral valve repair as adults with regard to preservation of valvular tissue, subvalvular apparatus, and ventricular geometry, leading to optimal valve and ventricular function. Furthermore, avoidance of mechanical prostheses is especially desirable in young children, in whom annular growth should be fostered and who may have little physical space for the prosthesis in the heart.

After pediatric mitral valve replacement, mismatch between native annulus and mitral prosthesis has been shown to be a risk factor for both early and late death (Caldarone et al. 2001; Kojori et al. 2004; Günther et al. 2000). The probability of mitral valve prosthesis re-replacement was demonstrated to be inversely related to the absolute size of the prosthesis initially implanted (Raghuveer et al. 2003). Finally, the cumulative risk generated by a lifelong commitment to anticoagulation should be avoided whenever possible.

Diagnostic tools are evolving rapidly and allow superior anatomic diagnosis and monitoring of the surgical repair. The range of surgical techniques modified from adult surgery into pediatric practice or specially developed for pediatric patients is large and allows tailoring of the surgical techniques to anatomic requirements.

Congenital mitral valve disease is rare and frequently associated with other cardiac malformations. Because it is usually complex, intervention is ideally postponed to allow time for annular growth and tissue maturity (Kruithof et al. 2007). This is usually considered to be safe, because depressed systolic ventricular function has been shown to recover after successful mitral valve surgery in pediatric patients (Krishnan et al. 1997; Murakami et al. 1999). Severe congestive cardiac failure refractory to maximal medical therapy, however, can result in surgery being undertaken in the first months of life.

Timing of Surgery

Indications for surgery vary according to the etiology and anatomy, the age of the patient, the size of the mitral valve annulus, and the clinical status. Neonates and infants with severe mitral valve disease are only considered for operation if they have severe symptoms. No symptoms are necessary if the valve can be repaired simply without annuloplasty (cleft mitral valve); for more complex valves, symptoms are usually present at the time of surgery. Surgical indications for patients with predominant mitral stenosis are dictated by symptoms only. No specific threshold figure for either pulmonary arterial pressure or transmitral gradient triggers a surgical indication if few or no symptoms are present (Oppido et al. 2008). An intervention before the first year of life is rarely needed in cases of isolated regurgitation.

Anesthetic Management

Mitral valve stenosis and the lesions obstructing flow at left atrial level (cor triatriatum, supramitral ring) essentially have the same requirements with regard to anesthetic goals and techniques. The main areas of concern are management of preload and afterload, heart rate, and pulmonary artery pressure (PAP), bearing in mind coexisting cardiac abnormalities. Pure congenital mitral stenosis is uncommon, and it is usually associated with other lesions, particularly Shone's complex (Shone et al. 1963).

Hypovolemia reduces the pressure gradient and hence flow across the stenotic lesion, while excessive fluid (and the Trendelenburg position) risks pulmonary edema. Afterload needs to be sufficient for adequate coronary artery perfusion, as well as

that of other organs. A slower heart rate allows a longer diastolic period for blood to cross the lesion, though too slow a rate reduces cardiac output. Tachycardia reduces diastolic time for flow through the lesion, and atrial fibrillation loses the invaluable atrial contraction propelling blood through it, as well as increasing heart rate. Rises in PAP reduce left-sided preload and can be caused by noxious stimuli—induction needs to be smooth, including intubation, and pain managed. Hypoxia, hypercarbia, and acidosis worsen pulmonary hypertension and should be controlled (allowing for any right to left cardiac shunts). A mild reduction of carbon dioxide partial pressure (PCO2) and rise in fraction of inspired oxygen (FiO2) are allowed. Maneuvers to reduce pulmonary hypertension such as high FiO_2, hyperventilation to reduce PCO_2, inhaled nitric oxide, phosphodiesterase inhibitors such as milrinone (including inhaled milrinone, with less systemic vasodilator effect), prostacyclin infusion, and sildenafil can collectively expose the pulmonary capillaries to high flow in the presence of back pressure from the stenotic lesion, risking pulmonary congestion and edema, and are thus best utilized post repair, where they are invaluable in aiding right ventricular performance post bypass and reducing the risk of pulmonary hypertensive crises, including in the postoperative period. Sildenafil (intravenous infusion of enteral) significantly reduces the incidence of pulmonary hypertensive crises when added to nitric oxide and is useful in preventing rebound pulmonary hypertension when weaning nitric oxide (see also chapters "Patent Ductus Arteriosus Devices" and "Double-Outlet Right Ventricle"). Nitric oxide is more effective in pulmonary hypertension caused by mitral stenosis in the child than in the adult. In Shone's syndrome, the anesthetic technique needs to target the predominant lesion, which can be difficult to determine. Maintenance of a patent ductus with a prostaglandin E2 infusion, if relevant, must be continued. Note that paracetamol is as effective in closing a patent ductus arteriosus (PDA) as ibuprofen (Ohlsson and Shah 2015).

Premedication, while smoothing induction, requires caution. Benzodiazepines can cause unwanted vasodilatation, opiates respiratory depression and worsening of pulmonary hypertension, and anticholinergics a rise in heart rate. Unless the stenotic lesion is severe and provided dosages are modest, these effects are unlikely to be significant. Topical local anesthetic cream at the sites of potential venous cannulation is useful.

In the absence of pre-existing venous access, induction with inhaled sevoflurane and securing venous access for administration of opiate and muscle relaxant are usual. High percentages of sevoflurane are significantly myocardial depressant. Halothane can cause unwanted arrhythmias, particularly nodal rhythm. Nitrous oxide causes modest rises in pulmonary artery pressure and increases the size of any air emboli. Intravenous induction with propofol, with its vasodilator properties, may need compensatory vasoconstrictor administration. Alpha agonists are usually used (metaraminol, phenylephrine) and cause reflex slowing of the heart rate, which is useful unless profound. Intravenous midazolam can cause significant vasodilatation. Ketamine is theoretically contraindicated, though heart rate and pulmonary artery pressure rises were only of the order of 10% in one study in children undergoing cardiac catheterization (Morray et al. 1984). Opiates such as fentanyl, sufentanil, and remifentanil can cause significant bradycardia, and pancuronium a tachycardia, the coadministration of both compensating for each other's effect, though unwanted tachycardia can predominate. Rocuronium and cisatracurium are acceptable muscle relaxants. Atracurium may be relatively contraindicated because of histamine release and consequent vasodilatation.

Monitoring is standard for cardiac surgery. PA catheters (5 F pediatric PA catheters are available) are controversial, potentially causing arrhythmias, thrombosis, pulmonary infarcts, and pulmonary artery (PA) damage. Wedge readings are not reliable left atrial pressure (LAP) estimates in the presence of pulmonary hypertension. PA and left atrial (LA) lines can be placed by the surgeon intraoperatively if deemed necessary. Transesophageal echocardiography (TEE) is vital to confirm the diagnosis, as a monitor of hemodynamics, to aid de-airing at the end of bypass and to assess the adequacy of surgical

repair. 3D echocardiography when feasible is superior in mitral valve assessment. Small 3D TEE probes are not yet available, but existing 3D probes are usable in larger children.

Maintenance with an opiate bias and low-dose inhalation agent is suitable. Post-cardiopulmonary bypass, measures to reduce pulmonary hypertension are applied, the purpose being to aid right ventricular function in the early postoperative period and help prevent pulmonary hypertensive crises. A PDE3 inhibitor, e.g., milrinone, is the usual initial inotrope. Levosimendan is as effective (Lechner et al. 2012), also lowers pulmonary artery pressure (PAP), and has the advantage of having an active metabolite with a long duration of action post infusion, typically 7 days.

Mitral valve surgery carries the risk of damage to the AV node, requiring AV pacing. The circumflex coronary artery can be compressed by annuloplasty material or prosthetic valve rings or occluded by encircling sutures (Azakie et al. 2003). This will manifest on the TEE with lateral LV wall hypokinesia. The circumflex artery can be visualized with multiplane TEE—at a transducer angle of about 105 degrees, follow the course of the left main stem coronary artery as it leaves the left coronary sinus and then the circumflex artery as the probe is rotated to the left. With color Doppler (set at a low frequency to enhance the signal, as flow is almost at right angles to the ultrasound beam), flow can be qualitatively assessed—turbulence for narrowing and cessation for occlusion. Care must be taken to follow the artery carefully, so as not to confuse it with the adjacent coronary sinus (Ender et al. 2010).

The PAP may return to normal or only partially fall immediately post repair. It may take weeks to months to normalize and may never become normal. Attempts to normalize pulmonary artery pressures postoperatively may result in unnecessary prolongation of ventilation and stay in the intensive care unit.

Mitral Regurgitation

Pure congenital mitral regurgitation is rare. It is associated with other pathologies such as LV dilatation of whatever cause, including cardiomyopathy, ALCAPA, or connective tissue disorders causing prolapse such as Marfan's syndrome and Ehlers-Danlos syndrome.

The main hemodynamic goals during anesthesia are a reduction in afterload, which decreases regurgitant flow in favor of forward flow and a mildly raised heart rate—bradycardia raises LVEDV, increasing mitral regurgitation. Patients are usually on an angiotensin-converting enzyme (ACE) inhibitor preoperatively to cause afterload reduction. These patients are frequently on diuretic therapy and may be hypovolemic as a consequence, with resultant reduction in LV filling. This should be judiciously corrected. PAP may be elevated, and increases must be avoided as for mitral stenosis.

Induction with sevoflurane is tolerated. Care is needed if ventricular function is poor. Pancuronium usefully increases the heart rate, but other muscle relaxants are acceptable. Maintenance with sevoflurane or isoflurane (which also increases heart rate) combined with opiates as per mitral stenosis above is well tolerated.

Monitoring is as for mitral stenosis above. Again, TEE is invaluable. Left ventricular function expressed as ejection fraction is misleading, since this is flattered by ejection into the low-pressure left atrium. Thus, in the presence of moderate or severe mitral regurgitation, an ejection fraction of less than 60% is likely to indicate LV dysfunction. This becomes apparent when the ejection fraction is reduced post repair. Inodilators such as milrinone or levosimendan are preferred over catecholamines, which raise afterload, and are also appropriate post-cardiopulmonary bypass.

Mitral regurgitation may coexist with mitral stenosis, in which case the anesthetic strategy favors the dominant lesion.

Surgical Techniques

Continuous cardiopulmonary bypass is established with bicaval and ascending aortic cannulation at mild hypothermia of 32 °C and pump flows of 150–200 mL/kg/min.

Intermittent antegrade cold blood cardioplegia is delivered every 20–30 min. Neither pro-

found hypothermia nor circulatory arrest is required for isolated mitral valve surgery.

Through a midline sternotomy, access to the mitral valve is gained either by a left atriotomy in the interatrial groove, transseptally, or with a combined approach. Exposure is optimized by cannulating the superior vena cava at a distance from the cavoatrial junction and the inferior vena cava adjacent to the cavoatrial junction. A self-retaining mitral valve retractor adapted to the size of the patient is used throughout. Visualization of the valve is further enhanced by mattress sutures in the posterior annulus and pulling the inferior vena cava more snugly up and to the left. The valve is then methodically inspected, and findings are integrated with the preoperative investigations, with care to note the following: the presence of a supravalvular mitral ring; annular diameter; leaflet texture and size; number, distribution, and morphologic characteristics of chordae and papillary muscles; nature of commissural tissue; and, finally, the presence of any accessory mitral valve tissue or tag in the interchordal spaces. The valve orifice is measured with Hegar dilators before and after repair, and the value is compared to predicted normal values indexed to the body surface area according to a modification of the sizes originally described by Kirklin and Barrat-Boyes (Kirklin and Barrat-Boyes 1993). Surgical techniques are tailored to the anatomy and mechanism of dysfunction (Table 3).

The spectrum of congenital mitral valve malformations ranges from the readily reparable anterior mitral leaflet cleft to the restrictive and challenging lesions of mitral stenosis. Whatever the abnormality, the incidence of associated heart defects is high (Almeida et al. 1988; Chauvaud et al. 1997; Coles et al. 1987) and can have a significant impact on the eventual clinical outcome.

Because of the significant short- and long-term problems with mechanical and bioprosthetic mitral valves in children (Borkon et al. 1986; Geha et al. 1979), considerable attention has been paid to mitral remodeling techniques (Chauvaud et al. 1997; Coles et al. 1987; Uva et al. 1995) for both incompetent and stenotic valves. This trend has lowered the perioperative mortality from as high as 21–43% for mitral valve replacement (Aharon et al. 1994; Kadoba et al. 1990) to as low as 0–5% for mitral valve repair (Chauvaud et al. 1997; Uva et al. 1995; Kadoba et al. 1990).

Table 3 Techniques for repair of congenital mitral valve anomalies

Resection of supravalvular stenosing ring
Valve
Resection of accessory mitral valve tissue
Closure of cleft/post-AVSD correction suture dehiscence
Patch closure of leaflet perforation
Leaflet resection
Sliding technique
Plication of redundant leaflet
Commissurotomy
Alfieri stitch
Annulus
De Vaga suture annuloplasty
Ring annuloplasty
Posterior pericardial annuloplasty
Anterior pericardial annuloplasty
Bilateral pericardial annuloplasty
Commissure plication annuloplasty
Chordae
Chordal shortening
Chordal transfer
Artificial chordate
Chordae prolongation
Chordae fenestration
Papillary muscle
Papillary muscle shortening: split and tuck in
Papillary muscle splitting

AVSD atrioventricular septal defect

Surgical Outcomes

The outcomes reported in the surgical literature in this group of patients are quite varied. Many authors have reported a significant incidence of poor outcomes, probably for a variety of reasons including complex mitral valve anatomy, frequent association with other heart defects, and a relative paucity of patients with these lesions, with consequently less experience with reconstructive techniques (Chauvaud et al. 1998; Uva et al. 1995; McCarthy et al. 1996). Other authors reported excellent results with a very low postoperative mortality and morbidity among patients

undergoing mitral valve surgery (Prifti et al. 2002; Stellin et al. 2010; Yoshimura et al. 1999).

Most authors have reported a significantly higher mortality rate—higher than 30%—among children undergoing mitral valve replacement (Zweng et al. 1989; Kadoba et al. 1990). However, other authors have reported acceptable early and long-term survival among children undergoing mitral valve replacement (Yoshimura et al. 1999).

In recent years, attempts to preserve the native mitral valve are preferred, especially in infants and young children. Mitral valve repair offers the advantages of avoiding thromboembolism, preserving chordal and subvalvular apparatus function, and potentially reducing the need for reoperation. Because of a wide spectrum of mitral valve lesions, which usually involve different sites of the valvular apparatus, multiple techniques of valve repair are required (Chauvaud et al. 1998; Uva et al. 1995; Prifti et al. 2002; Murakami et al. 1999; Aharon et al. 1994).

The need for ring annuloplasty procedure in the pediatric age group remains controversial. Chauvaud and associates (Chauvaud et al. 1998, 1997) used ring annuloplasty in children over 2 years of age, whereas other groups have demonstrated that other types of annuloplasty techniques can be employed successfully in children and the prosthetic rings are not indispensable for achieving favorable results (Uva et al. 1995; McCarthy et al. 1996; Zias et al. 1998).

Surgical repair of congenital mitral valve stenosis has been typically associated with greater postoperative mortality and morbidity (Chauvaud et al. 1997; Moran et al. 2000) and a higher reoperation rate compared with mitral valve repair for insufficiency (Stellin et al. 2000). The hammock mitral valve is the most difficult malformation to correct owing to the considerable amount of muscle found beneath the mitral valve leaflet causing severe left ventricular inflow obstruction (Chauvaud et al. 1997; Stellin et al. 2000). The hammock mitral valve is defined as a very dysplastic mitral valve, without tendinous chordae, with the apex of the papillary muscles having direct continuity with the leaflet tissue (Layman and Edwards 1967). In parachute and hammock mitral valve, the single papillary muscle is split delicately at the midline in two halves (Carpentier et al. 1976; Chauvaud et al. 1998; Prifti et al. 2002), thus increasing the excursion of the mitral valve during diastolic phase. When necessary a commissurotomy procedure is also performed.

For pediatric patients undergoing surgery for congenital mitral valve anomalies, age less than 1 year, hammock mitral valve, cardiothoracic ratio greater than 0.6, and associated cardiac anomalies are recognized risk factors for death or reoperation (Prifti et al. 2002). Uva and associates (Uva et al. 1995) reported excellent results in children less than 1 year of age undergoing mitral valve surgery, with a 7-year actuarial survival of 94%. On the other hand, Prifti and colleagues (Prifti et al. 2002) reported different results: 6 of 25 early deaths and 6 of 11 late deaths were patients less than 1 year old. In this series, the correction of the associated heart defects also increased the operative risk, probably because of significantly longer cardiopulmonary and aortic cross-clamping times, more complex anatomy, and left ventricular hypertrophy and impaired left ventricular function, particularly in cases with left ventricular outflow tract obstruction and ventricular septal defect.

Conclusion

Management of congenital anomalies of the mitral valve in the pediatric age group remains a therapeutic challenge for the wide spectrum of the morphological abnormalities. Improvements in preoperative evaluation, anatomical analysis of valvular lesions, anesthetic management, and surgical techniques have made it possible to obtain good results. Mitral valve reconstructive procedures in infants and children with congenital mitral valve anomalies are effective and reliable with low mortality and low incidence of reoperation rate. Mitral valve repair should always be attempted, especially in infants, despite the frequent severity of mitral valve dysplasia, to avoid the drawbacks of the currently available prostheses.

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Congenital Anomalies of the Aortic Valve

Christopher Denny and Premal M. Trivedi

Abstract

Valvular aortic stenosis represents the most common congenital anomaly of the aortic valve. As such, this chapter focuses predominantly on this lesion's diverse clinical presentations, pathophysiology, and current management strategies. Due to the marked differences between neonatal and childhood or adolescent valvular stenosis, anesthetic considerations are discussed in the context of each presentation. As a separate section within this chapter, supravalvular aortic stenosis is also reviewed. Though not indicated by its name, patients with supravalvular stenosis may also have stenosis at the valvular level (among other areas). Moreover, due to this lesion's association with anesthetic morbidity and mortality, it warrants special attention. To assist in risk stratification and anesthetic planning, an overview of potential risk factors and pitfalls is presented. Lastly, emerging therapies in the management of aortic valve disease are discussed.

Keywords

Critical aortic stenosis of the neonate
Ductal-dependent systemic perfusion
Prostaglandin E1 · Balloon aortic valvuloplasty · Surgical valvuloplasty
Aortic stenosis in the child and adolescent
Aortic valve replacement · Pulmonary autograft or Ross procedure · Bioprosthetic valves · Mechanical valves · Williams syndrome · Supravalvular aortic stenosis
Fetal interventions · Ozaki procedure

Valvular Aortic Stenosis

Congenital valvular aortic stenosis (AS) represents a continuum of anatomic lesions with equally broad clinical manifestations. Differences in the severity of valvular obstruction as well as the presence of associated lesions, such as hypoplasia of the left ventricle (LV), mitral valve, or aortic arch, account for this variability. The most severe end of the spectrum is represented by hypoplastic left heart syndrome (HLHS); on the other end is the individual with mild isolated valvular stenosis with otherwise normal cardiac structures. Clinical presentation

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can thus range from the critically ill neonate who is ductal-dependent to the asymptomatic child or adolescent (Affolter and Ghanayem 2014). Treatment strategies mirror the diversity of this disease process. Both catheter-based and surgical therapies are employed with the goal of optimizing native valve function until replacement is indicated; often, each therapy is utilized at different points in the management of the same patient.

Anatomy

The normal aortic valve is composed of three equally sized and mobile cusps that coapt centrally (Fig. 1). This arrangement is altered in abnormal aortic valves, where cusp size and number may vary, and partial or complete fusion of cusps can occur (Maizza et al. 1993; Roberts 1973). The result is a valve that may feature a smaller orifice, compromised leaflet mobility, and an eccentric

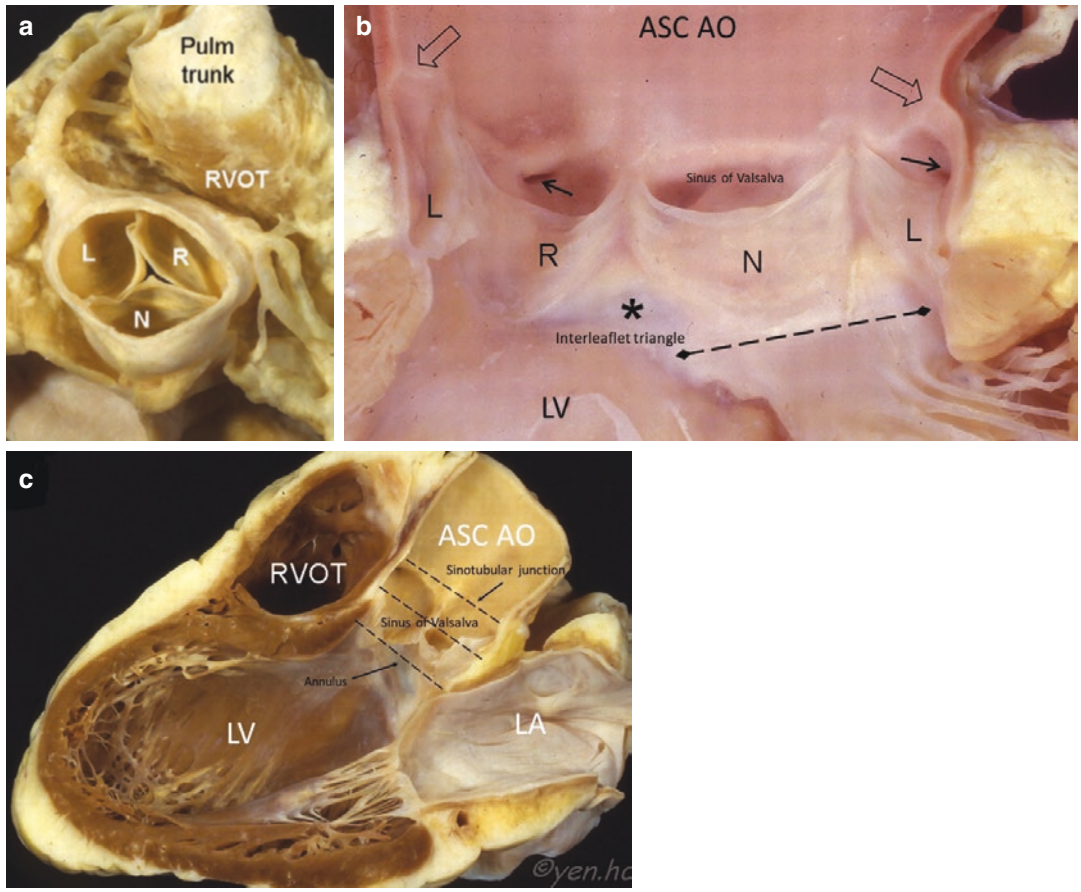

Fig. 1 Anatomy of the aortic valve and root. (**a**–**c**): Anatomy of the aortic valve and root (**a**) Aortic valve in cross section. Each cusp is marked with (*L*), (*R*), and (*N*) representing the left, right, and noncoronary cusps, respectively. The left and right coronary arteries can be observed arising from their respective cusp. Note also how each cusp forms a pocket, termed the sinus of Valsalva. (**b**) Aortic valve viewed with the left cusp transected longitudinally. *Open arrows* note the level of the sinotubular junction, distal to which the ascending aorta (*ASC AO*) begins. Solid black arrows demonstrate the ostia of the right and left coronary arteries. (*R*), (*L*), and (*N*) mark the respective coronary cusps. The triangular space between each cusp is identified as the interleaflet triangle or trigone. The dotted line represents the area of fibrous continuity between the aortic and mitral valves. (**c**) Long-axis view of the left ventricular outflow tract, the aortic root, and the ascending aorta. The aortic root includes all structures between the annulus and the sinotubular junctions (the valve leaflets, their attachments, and the interleaflet triangles) (Ho 2009)

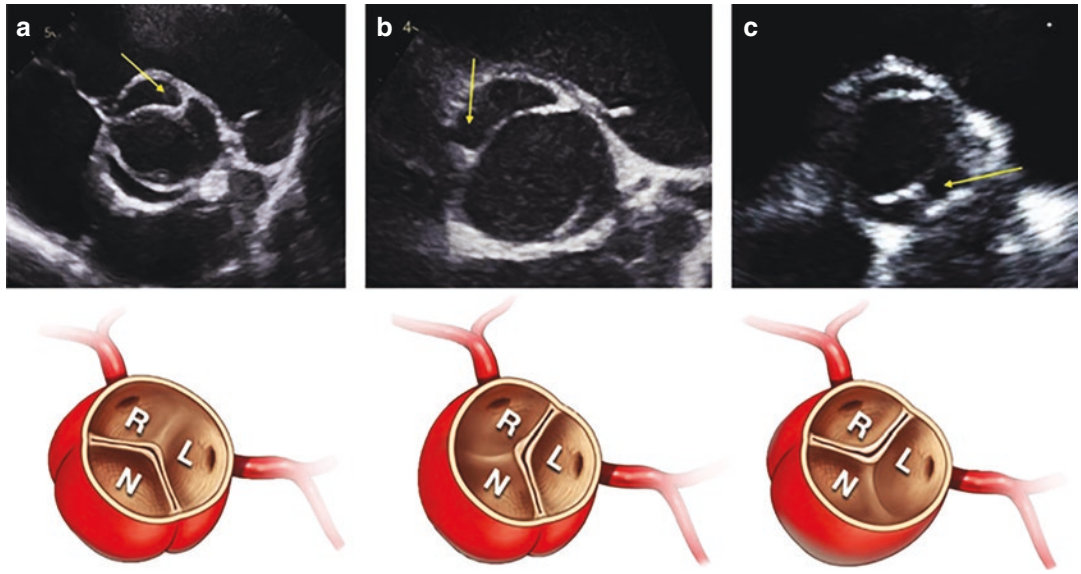

Fig. 2 Morphologic subtypes of bicuspid aortic valve. (**a**) Fusion of right and left coronary cusps. (**b**) Fusion of right and non-coronary cusps. (**c**) Fusion of left and non-coronary cusps. Arrow points toward the raphe. (Niaz et al. 2020 (Figure 1))

opening (Allen 2013). The sum of these characteristics determines the degree of stenosis observed. The most common among these abnormal morphologies is the bicuspid aortic valve (Allen 2013). Such a valve occurs in nearly 1.3% of the general population and is characterized by the partial or complete fusion of two of the aortic valve cusps (Larson and Edwards 1984; Roberts 1970). The conjoined and non-conjoined cusps may be of equal or asymmetric size, and their commissures may be partially fused (Fig. 2). Other anomalies of the aortic valve include a unicuspid valve in which two of the three commissures are fused, leaving only a single slit-like opening, and valves in which all three cusps are partially fused, creating a small central orifice. Occasionally, the valve leaflets defy characterization as either bicuspid or unicuspid and are simply described as immature and gelatinous (Elzenga and Gittenberger-de Groot 1985; Morris et al. 1990; Von Rueden et al. 1975). This tends to be true of the valves in neonates with critical aortic stenosis (Jonas and DiNardo 2004). Rarely, stenosis at the valvular level may result from a hypoplastic aortic annulus rather than any abnormality in the valve itself (Reeve and Robinson 1964).

Pathophysiology

Despite the immense variability in the anatomy and presentation of valvular AS, the pathophysiology has a common element: increased left ventricular afterload that ultimately results in an imbalance between myocardial oxygen demand and coronary perfusion. In utero, the increased afterload can result in different phenotypes depending on the severity of the stenosis and the developmental stage at which it occurs (Marantz and Grinenco 2015). Those with lesser degrees of obstruction that develop late in gestation often maintain an adequate left ventricular size which functions to accommodate a cardiac output in postnatal life (Allen 2013). Such individuals may present with failure to thrive or tachypnea as infants or may remain asymptomatic throughout childhood. Significant stenosis early in gestation, on the other hand, results in varying cardiac morphologies ranging from HLHS to severe left ventricular dilation (Affolter and Ghanayem 2014; Marantz and Grinenco 2015). The consequence of these more severe manifestations is a left ventricle (LV) that cannot support the systemic circulation.

Survival in postnatal life is then dependent on an atrial level shunt and a patent ductus arteriosus (PDA) ("ductal-dependent" for systemic blood flow). The right ventricle in these cases accepts the bulk or all of the cardiac output and ejects not only to the pulmonary arteries but also systemically through the ductus arteriosus. Ductal closure invariably results in cardiovascular collapse and death.

In the child or adolescent with aortic stenosis, the pathophysiology is comparable to that observed in adults in that myocardial hypertrophy develops in response to the increased afterload (Opie 2004). By Laplace's law (wall stress = pressure × radius/2 × wall thickness), hypertrophy acts to reduce wall stress while maintaining stroke volume and cardiac output, but at the expense of an increased left ventricular end-diastolic pressure (LVEDP) and increased myocardial oxygen demand (Donner et al. 1983). Coronary blood flow can thus be compromised as the gradient between aortic end-diastolic pressure and LVEDP decreases. Conditions that decrease diastolic blood pressure or increase myocardial oxygen demand can predispose the heart to ischemia, dysfunction, and arrhythmias. At greatest risk is the subendocardium due to the high compressive forces at this location and distance from the epicardial coronary arteries (Allen 2013). In utero, marked elevations in intracavitary pressures and increased myocardial oxygen demand can result in endomyocardial fibroelastosis (EFE), which can further contribute to postnatal ventricular dysfunction (Alsoufi et al. 2007). If untreated, aortic stenosis ultimately overwhelms the left ventricle's compensatory mechanisms and congestive heart failure ensues.

Critical Aortic Stenosis

Nearly 10% of patients with congenital valvular AS present within the first year of life (Brown et al. 2003; Hastreiter et al. 1963; McCrindle et al. 2001). Those who present in the first month often have critical aortic stenosis, a ductal-dependent lesion. Cardiogenic shock is the common clinical presentation resulting from inadequate systemic and coronary blood flow following ductal closure. Resuscitation entails the initiation of prostaglandin E1 (PGE_1) to re-establish systemic blood flow and the use of inotropic and ventilatory support as needed to maximize oxygen delivery.

Definitive management is guided by the central decision of whether to employ a strategy of single-ventricle palliation versus staged biventricular repair (Alsoufi et al. 2007). Guiding this decision are factors such as the degree of left-sided hypoplasia observed and the presence of associated lesions like ventricular septal defects, arch hypoplasia, or coarctation of the aorta. Those with severe hypoplasia of the left ventricle and mitral valve proceed down the pathway of single ventricle palliation or heart transplantation depending on institutional preference and organ availability. Alternatively, if the neonates were to have only isolated AS with otherwise adequately sized left-sided structures, a strategy conducive to biventricular repair would be chosen. The "gray area" between these two extremes, however, presents a dilemma. Several studies have attempted to identify predictive factors to assist in the process of assessing the adequacy of the LV to accommodate the systemic circulation (Hammon et al. 1988; Lofland et al. 2001; Rhodes et al. 1991; Schwartz et al. 2001). Commonly referenced is the regression equation developed by the Congenital Heart Surgeons' Society that is used to predict 5-year survival probability with Norwood-type palliation versus a biventricular approach (Lofland et al. 2001). Parameters assessed included patient age, grade of EFE, *z*-score of the aortic valve and left ventricular length, ascending aorta diameter, and the presence of significant tricuspid regurgitation. Underscoring the significance of appropriate initial therapy is data suggesting invariably worse outcomes when "crossover" between strategies is required (Rhodes et al. 1991).

Treatment

For neonates with isolated critical AS, initial therapy entails either balloon or surgical valvuloplasty to relieve the obstruction. No prospective randomized trials have been performed to

compare outcomes between these techniques, and retrospective studies have yielded mixed data (McCrindle et al. 2001; Rehnstrom et al. 2007; Siddiqui et al. 2013; Vergnat et al. 2019; Zaban et al. 2020; Herrmann et al. 2020). A recent meta-analysis comparing the two techniques demonstrated no difference in long-term survival, relief of obstruction, or rate of aortic valve replacement (Hill et al. 2016). However, a significantly higher rate of reintervention following balloon aortic valvuloplasty (BAV) was noted. Confounding comparisons of these two therapies has been the evolution of both catheter-based and surgical techniques. Whereas surgical repair was once limited to rigid aortic valve dilation or blade commissurotomy, current techniques are more refined and include resection of nodular dysplasia and reconstruction of the aortic valve leaflets (Fig. 3) (Siddiqui et al. 2013). Such repairs, however, require cardiopulmonary bypass and its

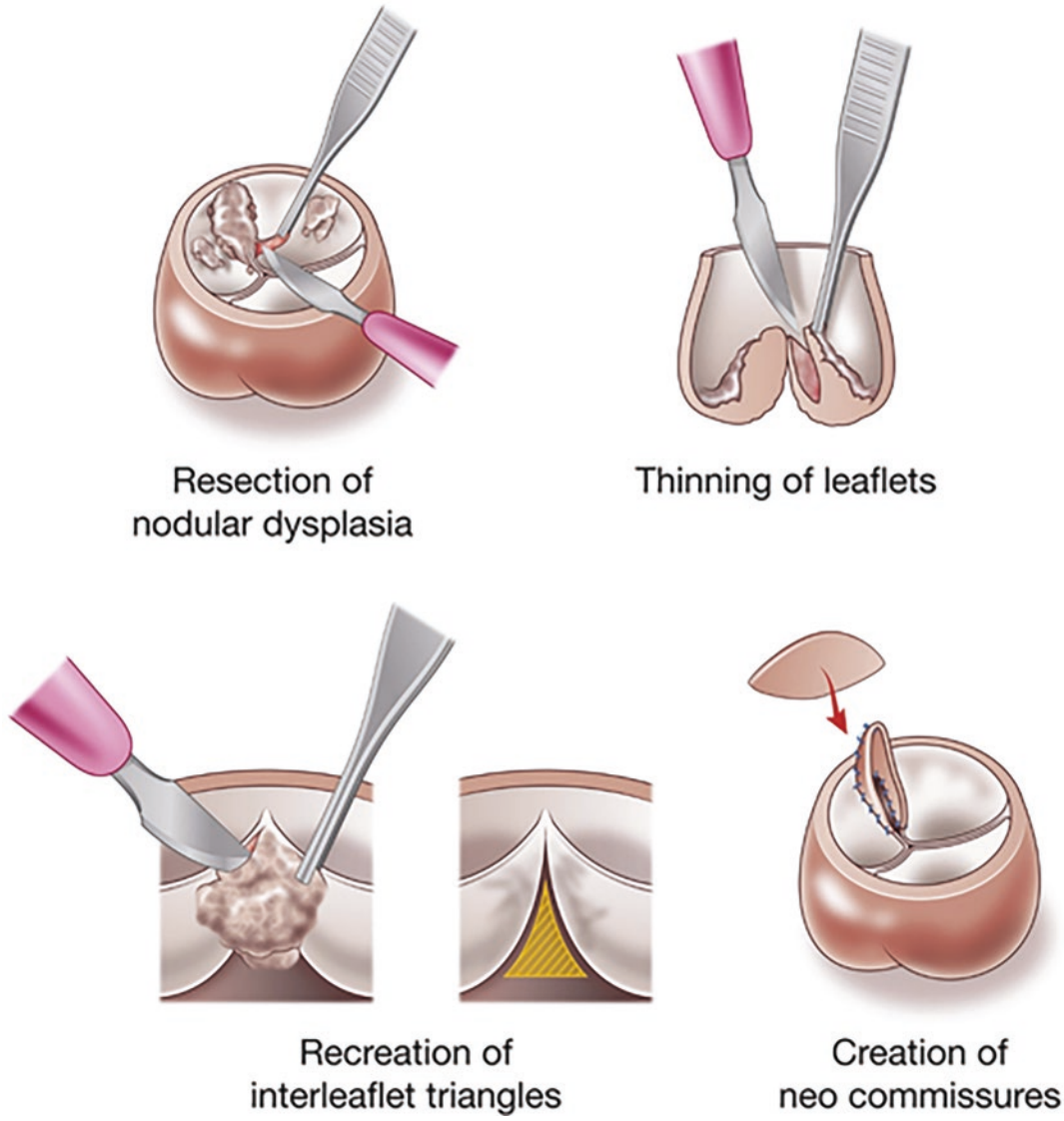

Fig. 3 Surgical techniques for the repair of congenital aortic stenosis in neonates and infants. (Siddiqui et al. 2013 (Figure 2))

associated morbidities. Similar advances have been made in catheter technology, with improvements in the balloons and wires used in valvular dilation (Stapleton 2014).

Technical considerations relevant to the anesthesiologist in patients undergoing balloon aortic valvuloplasty (BAV) include the vascular approach used and patient positioning (Stapleton 2014). The aortic valve can be accessed via the femoral vein, femoral artery, or right common carotid. If the femoral vein is used, the aortic valve is approached antegrade such that the catheter must traverse the atrial septum, mitral valve, and left ventricle in sequence. This route, however, is challenging due to the potential small size of the left-sided structures which can limit catheter advancement. Catheter-induced arrhythmias and obstruction to flow can also decrease cardiac output in an already tenuous patient (Daaboul et al. 2019). Consequently, the preferred approach to the aortic valve is retrograde through either the carotid, or more commonly, the femoral artery. While the carotid approach is more direct and expedient, its use can be associated with neurologic injury (secondary to catheter-associated decreases in cerebral blood flow or thromboembolic events). It is therefore reserved for the smallest of neonates in whom the risk of femoral artery injury exceeds that of the carotid (Stapleton 2014; Borghi et al. 2001; Choudhry et al. 2016). To facilitate access, the patient may be turned 180° away from the usual position (such that the airway is furthest from the anesthesiologist). Care with positioning of lines and the endotracheal tube (ETT) is necessary in this circumstance to minimize the risk of line displacement or kinking of the ETT.

While some degree of aortic insufficiency is expected following balloon dilation, the introduction of severe aortic insufficiency can be catastrophic. Fortunately, this complication is rare. One series reported a 2% incidence of severe insufficiency immediately post-ballooning (Brown et al. 2010; Petit et al. 2012). The additional volume load imposed on the left ventricle increases left ventricular end-diastolic pressure and, in concert with lower aortic end-diastolic pressure, may produce marked myocardial ischemia. Emergent valve repair or replacement is necessary in this circumstance to prevent myocardial infarction. Of note, even in those who have only minimal insufficiency following initial ballooning, progression may occur over time such that one-third of patients have moderate-to-severe regurgitation at 10 years post-procedure (Stapleton 2014). As BAV is a palliative procedure whose goal is not complete elimination but improvement of the stenosis, the need for reintervention is high. Over two-thirds of neonates undergoing BAV require either repeat ballooning or surgical intervention at 10 years following the procedure (Brown et al. 2010; McElhinney et al. 2005). Currently, procedural success is defined as a residual peak systolic ejection gradient <35 mm Hg and mild or less aortic regurgitation (Morray and McElhinney 2021).

Rarely, aortic valve replacement is necessary in the neonate or infant with critical AS (Alsoufi et al. 2007). Indications include the presence of complex multilevel left ventricular obstruction, significant aortic regurgitation that develops during balloon valvuloplasty, or stenosis refractory to balloon valvuloplasty or surgical valvotomy. Options for replacement include aortic valve homografts or the patient's own pulmonary valve (pulmonary autograft). No appropriately-sized mechanical valves exist for this population.

Homografts have drawbacks unique to the young and growing patient. Due to their lack of growth potential and propensity to become progressively stenotic due to calcific degeneration, homografts require interval reoperation for upsizing. Use of a pulmonary autograft (the Ross procedure) may be considered when the pulmonary valve is of an adequate size and without stenosis or regurgitation (Al-Halees et al. 2002; Bansal et al. 2015; Kadner et al. 2008; Nelson et al. 2015; Ohye et al. 2001; Williams et al. 2005). This operation entails removing the stenotic aortic valve and replacing it with the patient's own pulmonary valve. A homograft is then used to reconstruct the right ventricular outflow tract. The advantage of this procedure is that the pulmonary valve maintains its potential for growth in the aortic position, is durable, and does not require anticoagulation. Outcomes are poor,

however, in the neonatal and infant population, with mortality rates ranging from 12 to 75% (Buratto and Konstantinov 2021; Donald et al. 2020; Burkhart et al. 2020; Buratto et al. 2018; Brancaccio et al. 2014; Kadner et al. 2008; Kirkpatrick et al. 2008; Tan Tanny et al. 2013). This is partly attributable to how ill these patients are prior to this intervention.

Anesthetic Management

Irrespective of the initial therapy chosen, principles of anesthetic management focus on supporting myocardial function, balancing systemic and pulmonary blood flow, and optimizing oxygen delivery. In the neonate with critical AS presenting in cardiogenic shock, therapy consists of continuing PGE_1, inotropic and/or vasopressor support, and mechanical ventilation (Affolter and Ghanayem 2014). Both epinephrine and dopamine appear to be effective inotropes in neonates (Barrington et al. 1995; Valverde et al. 2006). Vasopressor support, while useful in maintaining diastolic and coronary perfusion pressure, may also compromise splanchnic perfusion and worsen left ventricular function by increasing afterload. The benefits of such agents must be weighed against the potential for these risks. In the neonate presenting in a compensated state (without respiratory or inotropic support), one should remain alert to the potential for instability with anesthetic induction and intubation. The LV in such patients is often dilated and dysfunctional. Consequently, our practice is to start an epinephrine infusion with induction to minimize hemodynamic instability.

When choosing ventilator settings, care should be taken to avoid increasing pulmonary blood flow at the expense of systemic and coronary perfusion. Increases in inspired oxygen or hyperventilation may decrease pulmonary vascular resistance, resulting in increased left-to-right shunting through the PDA in diastole. Diastolic hypotension (with subsequent myocardial ischemia) and reduced pulmonary compliance (due to the increased LVEDP associated with increased pulmonary blood flow) may ensue. In the subgroup of neonates with significant lung injury, however, increased inspired oxygen and aggressive ventilation may be necessary to achieve even marginal gas exchange.

The choice of anesthetic often includes a combination of opioids and benzodiazepines. Most drugs can be used safely, however, assuming that doses are titrated to maintain hemodynamics while providing analgesia and minimizing oxygen consumption. Given the potential for blood loss and arrhythmias with intervention, packed red blood cells and defibrillation pads should be readily available.

Monitoring entails the usual ASA standards: a 5-lead electrocardiogram, non-invasive blood pressure cuff, esophageal temperature probe, pulse oximetry, and end-tidal CO_2. For patients undergoing BAV, additional arterial access is commonly placed to assess hemodynamics during ballooning and to facilitate post-procedural monitoring. ST changes or diastolic hypotension following angioplasty should alert one to the possibility of new and significant aortic insufficiency. If the carotid artery is used for access, near-infrared cerebral oximetry can promptly alert one to access-induced changes in cerebral perfusion.

The Child or Adolescent with Valvular Aortic Stenosis

In contrast to the neonate with critical AS or infant with progressive heart failure, older children and adolescents with valvular obstruction are commonly asymptomatic (Allen 2013). This reflects the milder degree of stenosis initially present in these individuals (Tchervenkov et. al. 2012) as well as the relatively slow rate of stenotic progression (Allen 2013). On average, the transvalvular gradient increases by 1 mm Hg/year (Davis et al. 2008); the exception occurs in children whose somatic growth greatly exceeds that of their stenotic aortic valve. When symptoms do occur, easy fatigability is most often reported (Ellison et al. 1976). Dyspnea on exertion, angina, and syncope can also occur as in adults, but are relatively uncommon even in those with severe stenosis (Wagner et al. 1977).

Table 1 Categorizing severity of valvular aortic stenosis (Maron and Zipes 2005)

	Catheter-derived peak-to-peak gradient	Mean Doppler gradient	Peak instantaneous Doppler gradient
Mild	<30 mm Hg	<25 mm Hg	<40 mm Hg
Moderate	30–50 mm Hg	25–40 mm Hg	40–70 mm Hg
Severe	>50 mm Hg	>40 mm Hg	>70 mm Hg

Assuming normal ventricular function and no shunting lesions

Clinical severity is assigned based on catheter-derived or Doppler-derived gradients (Table 1, Maron and Zipes 2005). Peak-to-peak pressure gradients are catheter-derived and reflect the difference between peak left ventricular and peak aortic pressures. Peak instantaneous gradients, on the other hand, are Doppler-derived and reflect the point in time in which the velocity of blood across the aortic valve is greatest. These pressure gradients thus provide different data points and should not be used interchangeably (Beekman et al. 1992).

Factors influencing the gradient beyond the extent of valvular stenosis include the patient's ventricular function and hemodynamic state at the time of measurement. Depressed ventricular function serves to underestimate one's gradient, whereas increased contractility and tachycardia may significantly increase the gradient recorded. Likewise, gradients obtained under deep sedation or anesthesia can underestimate the extent of obstruction present during normal activity. Such variables require consideration when determining the severity of valvular stenosis.

Timing of intervention is guided by an assessment of the measured gradient, ventricular function, symptoms, and the patient's level of activity (Allen 2013; Feltes et al. 2011). Those with peak-to-peak gradients >50 mm Hg have an absolute indication for intervention even if asymptomatic given the increased and progressive risk of myocardial injury and sudden cardiac death. Individuals who wish to be active, have symptoms of angina or syncope, or have ischemic changes on exercise stress testing are directed toward intervention even with peak-to-peak gradients between 40 and 50 mm Hg. Intervention is not recommended in the asymptomatic patient with a peak-to-peak gradient <40 mm Hg unless ventricular function is also depressed.

Treatment

As with neonates and infants, initial management options in children and adolescents include BAV or surgical repair (Fig. 4). Whereas BAV offers the benefit of less invasiveness, it is also associated with a higher rate of reintervention, a lower median time to reintervention, and a lower gradient reduction relative to surgical repair (Bouhout et al. 2018; Soulatges et al. 2015; Brown et al. 2012; Loomba et al. 2015). There is the also the concern that prior balloon valvuloplasty may reduce the durability of subsequent surgical repair of the aortic valve (Wilder et al. 2016; Vergnat et al. 2017). Nonetheless, as acute outcomes, survival, and need for aortic valve replacement appear comparable between these two therapies, BAV remains the preferred intervention at many centers (Hill et al. 2016; Morray and McElhinney 2021).

When valve replacement is indicated due to either progressive regurgitation or recurrent stenosis refractory to ballooning or attempts at surgical repair, options include the use of a mechanical valve, bioprosthetic valve, or pulmonary valve autograft. None are ideal. Both mechanical and bioprosthetic valves commit the child to future valve replacement due to their inability to grow (Gallo et al. 1988; Clarke et al. 1993; Mavroudis and Backer 2013). Mechanical valves, moreover, require anticoagulation and can result in bleeding or thromboembolic complications (Allen 2013; Mazzitelli et al. 1998). The pulmonary autograft or Ross procedure, while providing a durable and functional neo-aortic valve, also requires subsequent reoperation. Compared to neonates and infants, reoperation on the neo-aortic valve is more common in children and adolescents undergoing the Ross procedure; reintervention on the right ventricular outflow tract (for addressing conduit stenosis and/or regurgitation), however, is less common (Nelson et al. 2015).

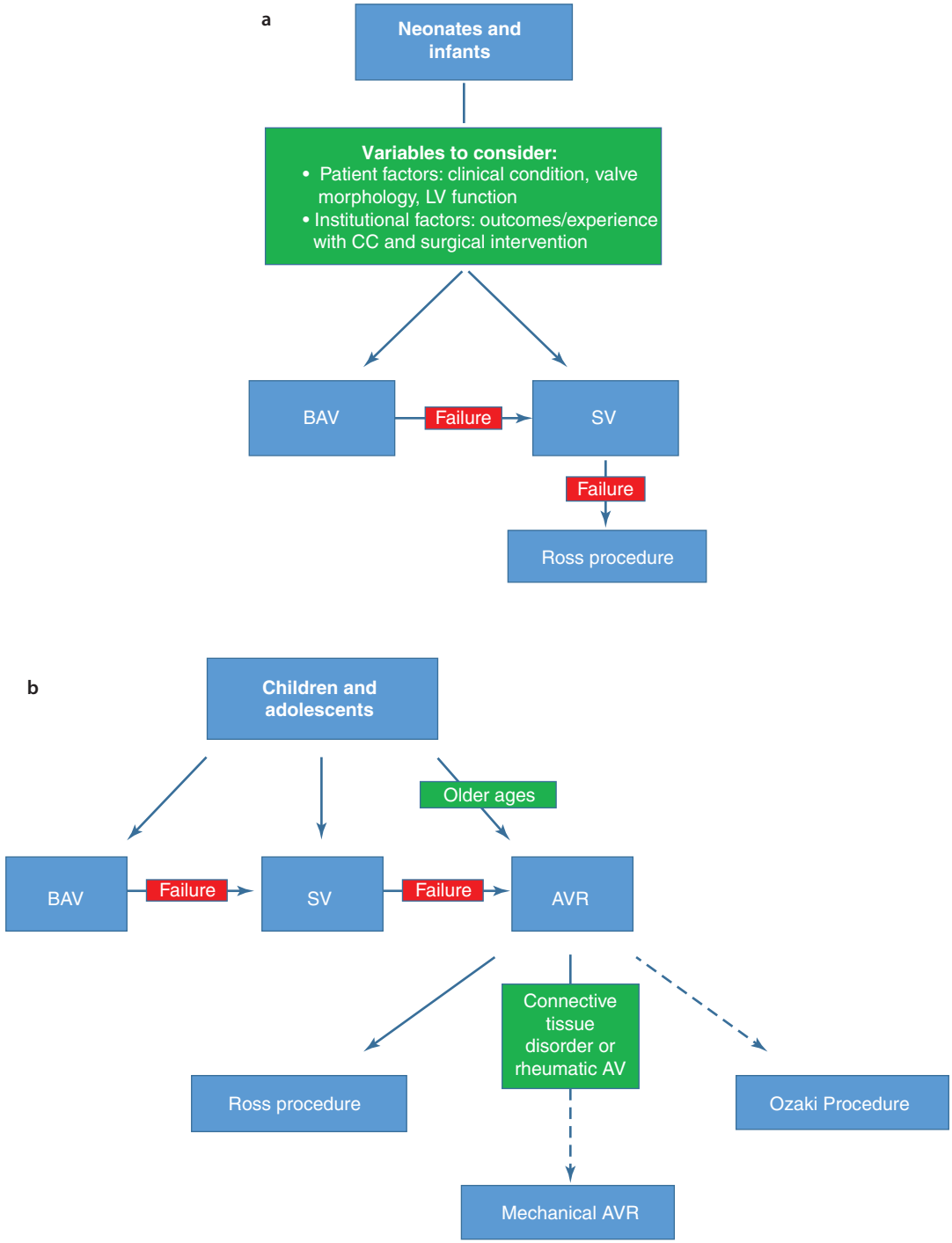

Fig. 4 Proposed management algorithm for pediatric patients with aortic valve disease. Proposed management algorithm for pediatric patients with aortic valve disease. Dotted line: area of significant controversy. *AS* aortic stenosis, *AV* aortic valve, *AVR* aortic valve replacement. (**a**) Neonates. (**b**) Children and adolescents (Bouhout et al. 2018 (Figure 2))

Anesthetic Management

Anesthetic technique and risk assessment can be guided by the patient's left ventricular function, gradient severity, and co-morbidities. Most often ventricular function is preserved in this age group regardless of the gradient and anesthetics are consequently well-tolerated. General principles include ensuring an adequate coronary perfusion pressure through maintaining euvolemia, afterload, and contractility while targeting a normal-to-low heart rate. Extended periods without fluid intake or the use of agents that significantly diminish preload or afterload can place the patient at risk for hypotension with the induction of anesthesia. Minimizing the fasting period or placing a preoperative intravenous (IV) catheter to give fluids can help decrease this risk. In the individual with significant aortic stenosis, low diastolic pressures can quickly produce a sequence of myocardial ischemia, ventricular dysfunction, bradycardia, and ultimately cardiac arrest. Alternatively, significantly increased contractility and tachycardia due to an inadequate level of anesthesia can also cause subendocardial ischemia. Careful titration of drugs while monitoring hemodynamics is thus essential to balance myocardial oxygen demand and supply.

For patients undergoing BAV, additional considerations deserve discussion. Older patients with a borderline indication for intervention based on Doppler-derived gradients may present for cardiac catheterization to provide the definitive peak-to-peak gradient. In such cases, light sedation may be preferable to general anesthesia during this diagnostic portion since the latter may lead to an underestimate of the actual gradient. Our preference includes the child with a borderline indication for intervention based on Doppler-derived gradients and the potential use of rapid right ventricular pacing. Our preference otherwise is to use general endotracheal anesthesia to avoid the risk of movement with balloon dilation that may increase the risk of aortic valve injury. Importantly, rapid right ventricular pacing may be used to reduce stroke volume and minimize balloon movement during inflation in older patients. The resulting decrease in cardiac output is typically well-tolerated in those with preserved LV function, but may necessitate treatment with phenylephrine to expedite recovery. As the approach to the aortic valve will most commonly be through the femoral artery, the need for a separate arterial line for dedicated blood pressure monitoring is dictated by the patient's baseline LV function and co-morbidities.

Supravalvular Aortic Stenosis

While rare in the general population, supravalvular aortic stenosis (SVAS) occurs in nearly 45–75% of those with Williams-Beuren (Williams) syndrome (Collins 2013; Eronen et al. 2002). Other familial or sporadic forms account for the remainder of SVAS cases observed. Though the obstruction generally occurs at the level of the sinotubular junction, all areas of the aortic root can be affected, including the coronary arteries and aortic valve leaflets. Such multilevel obstruction substantially increases the risk of myocardial ischemia, cardiac arrest, and sudden death during anesthesia (Burch et al. 2008; Matisoff et al. 2015; Twite et al. 2019; Bird et al. 1996). The underlying defect is an abnormality in the elastin gene resulting in a decrease in elastin within vessel walls (Nickerson et al. 1995; Jiao et al. 2017; Twite et al. 2019). Other large vessels can therefore also be involved, including the descending aorta and pulmonary, brachiocephalic, mesenteric, and renal arteries (Burch et al. 2008; Pober et al. 2008). This variability in the vessels affected and the subsequent risk imparted illustrate the complexity of this disease and the challenge in managing it.

Anatomy and Pathophysiology

Supravalvular aortic stenosis is classified as either diffuse or localized (Mavoroudis and Backer 2013). The majority have stenosis localized to the sinotubular junction, resulting in the characteristic hourglass appearance of the ascending aorta. Approximately 25% of patients, however, have diffuse stenosis that can extend to

the aortic arch and beyond (Kim et al. 1999; Stamm et al. 1997). Thickening at the sinotubular junction produces a narrowed aortic outflow that results in an increased afterload on the left ventricle, hypertension in the aortic root, and limited excursion of the aortic valve leaflets in systole (Mavroudis and Backer 2013). The valve cusps, moreover, can become adherent to the enlarging ridge (Flaker et al. 1983; Peterson et al. 1965). When this occurs, blood flow into the sinuses of Valsalva, and thus coronary blood flow, can be restricted. Compounding the potential for diminished coronary blood flow are anomalies of the coronary arteries themselves. Due to the severe hypertension in the aortic root, coronary artery disease can develop, with the most profound changes occurring proximally (Kim et al. 1999; Stamm et al. 1997). Moreover, the same process that leads to thickening of the aorta can also extend to and narrow the coronary ostia, further limiting coronary flow (Meairs et al. 1984).

Supravalvar pulmonary stenosis (SVPS) commonly occurs in combination with SVAS and is observed in nearly 83% of those with Williams syndrome (Bruno et al. 2003; Collins 2013; Eronen et al. 2002). This stenosis tends to be peripheral and diffuse, but central or discrete focal stenosis can also occur. In contrast to SVAS which tends to progress with time, SVPS may spontaneously regress (Giddins et al. 1989; Wren et al. 1990).

Congenital abnormalities of the aortic valve are uncommon, but, as noted previously, can develop due to exposure to high systolic pressures and adherence of the valve cusps to the thickened sinotubular ridge. Both valvular stenosis and insufficiency can occur.

These changes, in sum, produce a patient with increased myocardial oxygen demand and diminished myocardial oxygen supply. As in the patient with valvular AS, left ventricular hypertrophy develops in response to the increased afterload. The patient with SVAS, however, may also have right ventricular hypertrophy due to supravalvular pulmonary stenosis. Both ventricles, then, can be at risk for ischemia. Compounding this problem are the multifactorial reductions in coronary blood flow. Decreases in diastolic blood pressure or increases in myocardial demand can thus lead to biventricular subendocardial ischemia, fibrosis, papillary muscle infarction, and sudden death.

Treatment

Surgery is the recommended therapy for SVAS. Balloon dilation and stenting have been reported (Jacob et al. 1993; Pinto et al. 1994), but have significant risk due to the proximity of both the coronaries and aortic valve to the supravalvular obstruction (Allen 2013). This modality is generally reserved for the management of isolated peripheral pulmonary stenosis (Mavroudis and Backer 2013). Indications for surgery include a Doppler-derived mean gradient of greater than 40–50 mm Hg or the presence of symptoms (Mavroudis and Backer 2013). Given the progressive nature of this disease, early surgery is often recommended. Preoperative evaluation may include echocardiography, computed tomography, cardiac catheterization, or magnetic resonance imaging. The benefits of such procedures, though, must be weighed against the risks of anesthesia (if needed to complete these studies).

Preferred surgical techniques to address SVAS include enlarging the aorta using either an inverted bifurcated patch (a Doty or "pantaloon" patch) or three individual patches in each of the sinuses of Valsalva (a Brom aortoplasty) (Doty et al. 1977; Hazekamp et al. 1999) (Fig. 5). A technique utilizing autologous tissue in place of three patches, termed the "slide aortoplasty," has also been described (Myers et al. 1993). In patients with discrete obstruction, resection of the stenosis with only an end-to-end anastomosis can be performed. For cases of more diffuse stenosis, a combined ascending aorta and arch patch plasty may be needed (Mavroudis and Backer 2013). Lastly, for those individuals with simultaneous involvement of the coronary arteries and aortic valve, the Ross procedure can be offered. Given that all of these procedures are performed with cardiopulmonary bypass, any associated lesions such as pulmonary stenosis are also addressed at the time of aortic repair.

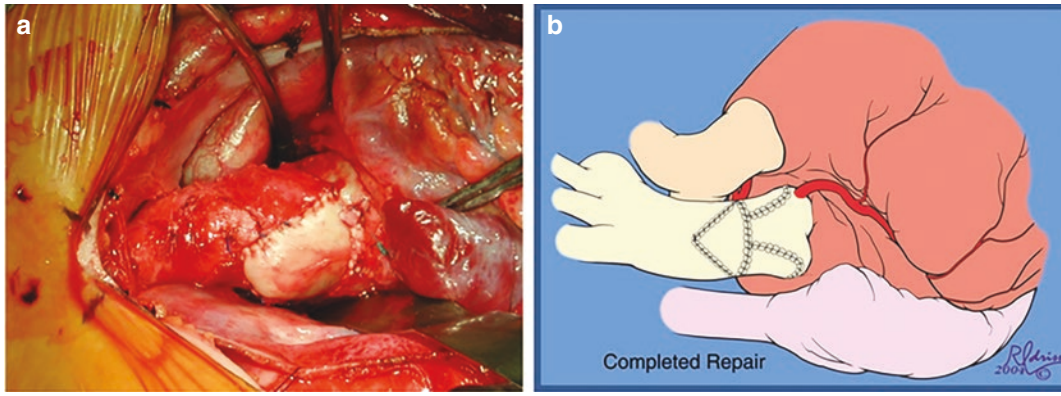

Fig. 5 Brom Aortoplasty for repair of supravalvular aortic stenosis. (**a**) Intraoperative photograph of completed Brom aortoplasty. (**b**) Illustration of completed repair. (Monge et al. 2018 (Figure 4))

Table 2 Characteristics associated with low-, moderate-, and high-risk patients with Williams syndrome

Low risk	Moderate risk	High risk
Normal EKG	Mild stenosis of a branch pulmonary artery	Severe SVAS (>40 mm Hg)
Normal echocardiogram	Hypertension	Symptoms or EKG findings consistent with ischemia
Minimal extracardiac anomalies	Mild-to-moderate SVAS (<40 mm Hg)	Coronary disease demonstrated on imaging
	Other mild cardiac anomalies (e.g., ventricular septal defect)	Severe left ventricular hypertrophy
	Repaired SVAS or SVPS without residual gradients	Biventricular outflow tract disease of ≥moderate severity
	Mild left ventricular hypertrophy	Prolonged QTc (≥500 ms) on EKG and/or pre-procedural arrhythmia
	Mild-to-moderate SVPS in isolation	Diffuse stenosis of the thoracic aorta
	Significant extracardiac disease such as difficult airway or severe gastroesophageal reflux	

Adapted from Matisoff et al. (2015) and Collins et al. (2017)

Risk Assessment

Although no prospective studies have evaluated risk factors for anesthesia in patients with SVAS, consensus opinion based on experience and known risk factors for myocardial ischemia can be offered (Matisoff et al. 2015; Collins et al. 2017). Those at greatest risk of anesthesia-related cardiac arrest appear to be patients with (1) biventricular outflow tract obstruction, (2) moderate-to-severe SVAS (>40 mm Hg), (3) documented coronary anomalies, and (4) symptoms or electrocardiogram signs consistent with ischemia, such as QT prolongation or ST-T wave abnormalities (Table 2). While the majority of patients may be asymptomatic, symptoms including angina, syncope, dyspnea on exertion, and diaphoresis with feeds have been noted in those with severe disease.

Anesthetic Management

As for any complex patient, multidisciplinary communication and planning are needed to optimize outcome (Collins et al. 2017). The patient with SVAS should be evaluated prior to the day of surgery, and contingency plans for those who

are high-risk, including the deployment of extracorporeal membrane oxygenation (ECMO) in the event of cardiac arrest, should be discussed. An assessment of organ systems beyond the heart and vasculature may also yield pertinent findings. In Williams syndrome, evidence of gastrointestinal reflux, hypercalcemia, hypothyroidism, and impaired glucose tolerance may be present (Matisoff et al. 2015; Twite et al. 2019; Staudt and Eagle 2021). Mandibular hypoplasia and malocclusion can also be observed and predispose to a difficult tracheal intubation.

Hemodynamic goals focus on maintaining preload, afterload, and contractility while avoiding tachycardia. Hypotension is aggressively avoided as lower blood pressures are much more poorly tolerated than higher ones. Ensuring adequate preoperative hydration is critical, and this can be achieved either through minimizing the period of fasting or obtaining intravenous (IV) access for fluid administration. In the absence of an IV, premedication with oral midazolam can reduce anxiety and thus decrease the risk of myocardial ischemia associated with tachycardia or hypertension. Oral ketamine (3–5 mg/kg) may also be used for this purpose or to facilitate obtaining intravenous access prior to induction. Though ketamine has the potential to increase heart rate, it also maintains contractility and systemic vascular resistance (SVR). Induction of anesthesia can be achieved with either inhalational or intravenous agents (or a combination of the two); it should be noted, however, that in high-risk patients, cardiac arrest has occurred even with low and incremental dosing of sevoflurane (Burch et al. 2008). If using an inhalational approach, the minimal dose of sevoflurane needed to obtain IV access should be used, and expert assistance to facilitate prompt IV access should be available. The sevoflurane dose can be reduced thereafter. Options for IV induction agents include etomidate, ketamine, fentanyl, and midazolam (Andrzejowski and Mundy 2000; Burch et al. 2008; Horowitz et al. 2002; Kohase et al. 2007; Matisoff et al. 2015; Medley et al. 2005). Any number of agents can be used to maintain anesthesia, but a balanced anesthetic with volatile agent and narcotic that allows for the preservation of SVR and contractility may be ideal.

Because of the rapidity with which decompensation can occur, vigilance is needed to identify initial signs of myocardial ischemia, most commonly heralded by ST changes. Phenylephrine should be administered to increase SVR if ST changes are observed, and either a phenylephrine or vasopressin infusion can be initiated prophylactically once additional IV access is obtained to maintain SVR. In the event of an impending or actual cardiac arrest, epinephrine (and other standard resuscitation drugs) should also be available along with blood for the priming of an ECMO or bypass circuit. Beyond the induction period, other times of risk that merit increased vigilance include emergence (in non-bypass cases) due to the potential for hypertension, tachycardia, hypercapnia, and hypoxemia.

Those with a history of SVAS or SVPS who present for noncardiac surgery following repair should be assessed for any residual gradients or persistent symptoms. Such patients, and particularly those with a history of diffuse SVAS, can remain at risk for anesthesia-related hemodynamic compromise even after aortic reconstruction. Preoperative planning for such patients should include not only a discussion of intraoperative strategy but also preoperative admission for hydration and postoperative disposition.

Emerging Therapies in the Management of Congenital Aortic Stenosis

Fetal intervention on developing AS and the adaptation of the Ozaki procedure, or aortic valve neocuspidization (AVNeo), to the pediatric population are relatively recent additions to the armamentarium of congenital AS management.

Fetal Intervention

With the advent of fetal echocardiography, it was observed that isolated AS could progress to HLHS in a subset of patients in utero (Friedman and Tworetzky 2020; Allan et al. 1989; Danford and Cronican 1992). To halt this progression and increase the likelihood of a postnatal biventricular circulation, fetal balloon aortic valvuloplasty was proposed (Fig. 6).

Patients are selected for this procedure based on two major criteria (Friedman and Tworetzky 2020). First, the fetus must be deemed highly likely to develop HLHS from the initially observed AS. Echocardiographic characteristics assist in this determination. Examples include moderately depressed (or worse) LV systolic function, bidirectional or left-to-right shunting across the foramen ovale (which should be right-to-left in utero), retrograde aortic arch flow, and monophasic mitral valve inflow (Friedman et al. 2018; Hunter et al. 2015; Makikallio et al. 2009; McElhinney et al. 2005). Second, the LV must be deemed capable of adapting to support the systemic circulation following intervention. Factors associated with adequate LV recovery include a higher pre-procedure LV pressure, larger ascending aorta *z*-score, and indices of more normal LV diastolic function such as a longer mitral valve inflow time (Friedman and Tworetzky 2020; Friedman et al. 2018).

Procedural success is defined by the presence of improved antegrade flow across the aortic valve and/or new aortic regurgitation (Friedman and Tworetzky 2020). In recent years, procedural success has been reported as high as 94% with a fetal demise rate of 6% (Tworetzky et al. 2004; McElhinney et al. 2005). No major maternal complications were noted in the Boston Children's series of 194 cases. In this same cohort, biventricular circulations were achieved in 41% of all liveborn patients, with a more recent higher rate of 59% (Friedman et al. 2018). Medium- and long-term survival are not yet available, however, and the incidence of comorbidities, such as progressive LV diastolic dysfunction and restrictive LV physiology (with subsequent left atrial and pulmonary hypertension), remains to be determined.

Application of the Ozaki Procedure to the Pediatric Population

The Ozaki procedure was first described in and developed for adult patients who required primary aortic valve replacement (Ozaki et al. 2014). The procedure aims to reconstruct the aortic valve using autologous pericardium, and offers an alternative to mechanical, homograft, and bioprosthetic valves. Survival and freedom from reoperation at 10 years in this predominantly adult population (ages 13–90 years) were 86 and 95%, respectively (Ozaki et al. 2018).

In 2021, Baird and colleagues were the first to report their experience in adapting the Ozaki procedure to the pediatric population (Baird et al. 2021). In their series, 57 patients with a median age of 12.4 years underwent three-leaflet AVNeo (Fig. 7). The underlying aortic valve disease included regurgitation (24), stenosis (6), and mixed regurgitation and stenosis (27). Thirty-four had prior aortic valve repairs and five had replacements. Four had truncal valves. At median follow-up of 8.1 months, 96 and 91% had less than moderate regurgitation and stenosis, respectively. Freedom from reoperation at 1.5 years was 91%. There were no hospital mortalities and two deaths (3.5%) following discharge.

Due to the relatively short-term follow-up, definitive recommendations on patient selection, outcomes, and complications remain pending. Current limitations include (1) the technical challenges of the surgery in the pediatric population (specifically the potential need for annular or root enlargement/reduction in addition to valve reconstruction), (2) the optimal tissue to use for leaflet construction when autologous pericardium is unavailable (as can be the case in redo sternotomies), (3) valve function in the setting of somatic growth (the treated pericardium does not have growth potential), and (4) the optimal anticoagulation strategy to minimize early thromboembolic complications (Karmalou et al. 2021; Baird et al. 2020).

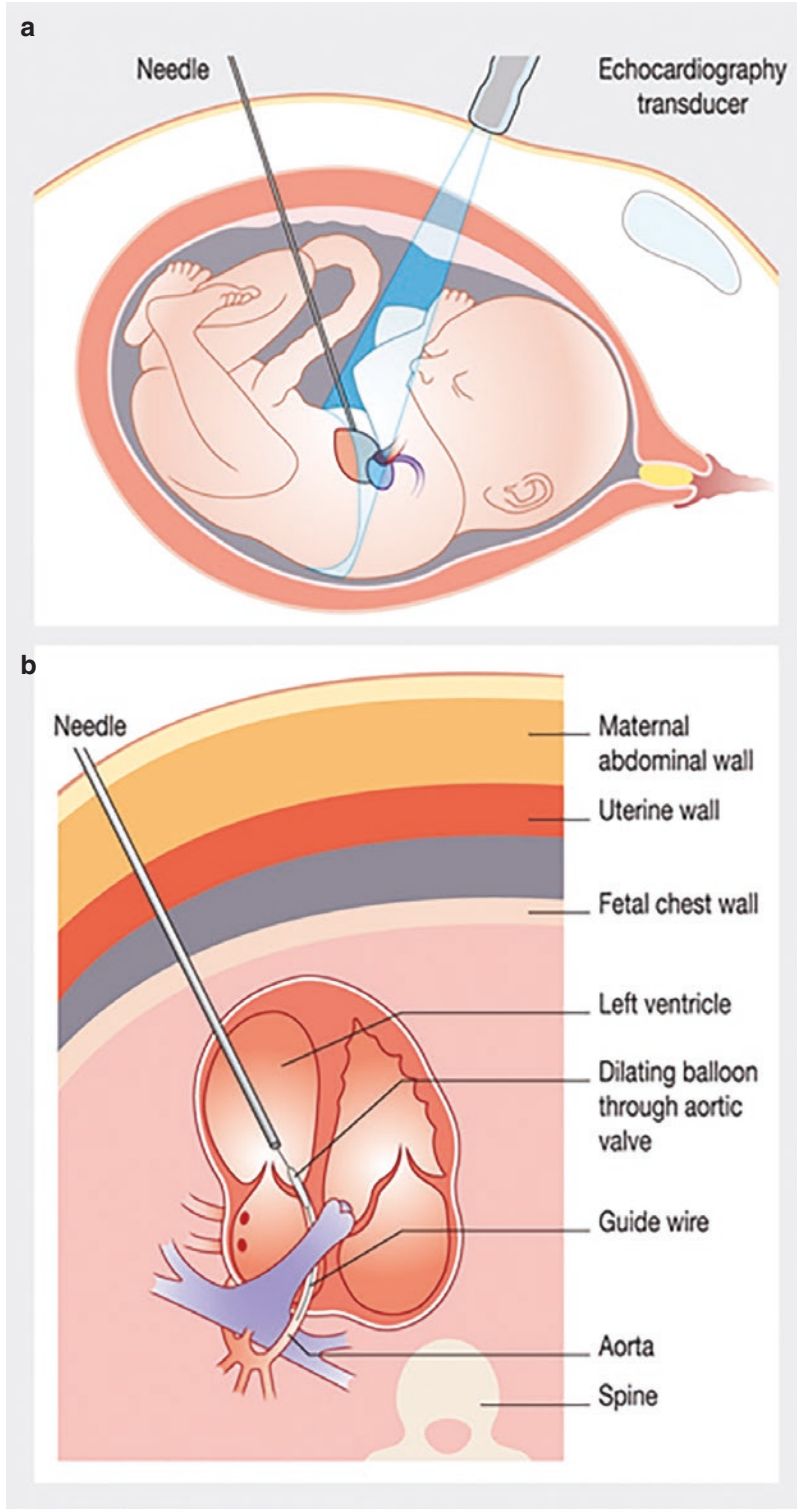

Fig. 6 Fetal Aortic Balloon Valvuloplasty. (**a**) Needle placement into the fetal left ventricle guided by transthoracic echocardiography. (**b**) Deployment of guidewire and balloon across the stenotic aortic valve. (Friedman and Tworetzky 2020 (Figure 1))

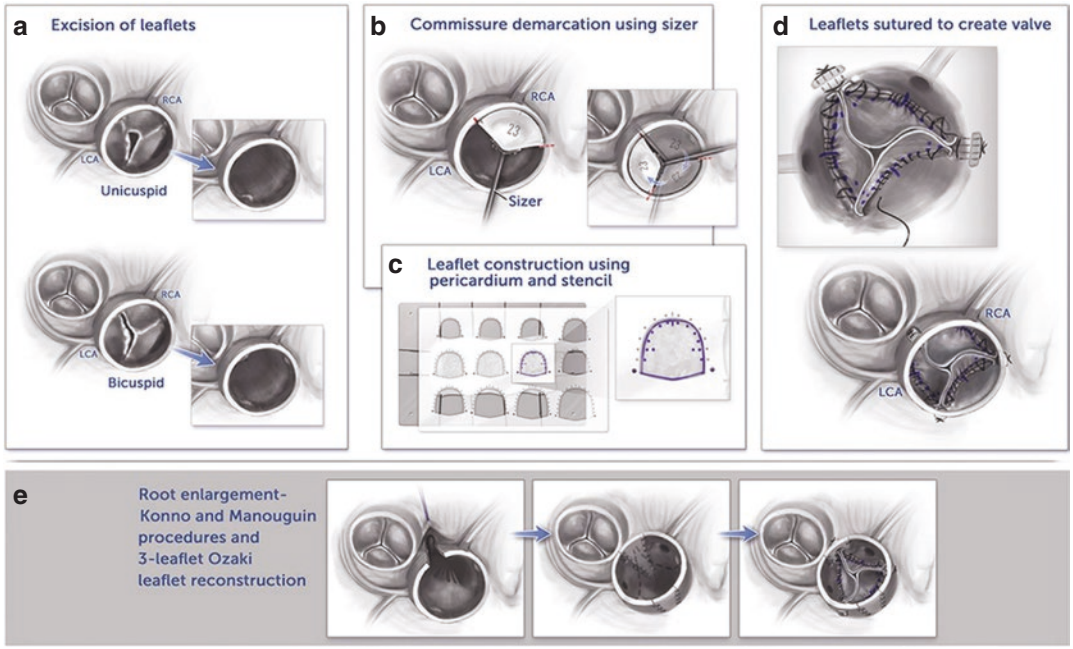

Fig. 7 Ozaki Procedure in children. (**a**) Excision of leaflets. (**b**) Commissure demarcation using sizer. (**c**) Leaflet construction using pericardium and template. (**d**) Leaflets sutured to annulus. (**e**) Aortic root enlargement with Konno and Manouguian procedures. *RCA* right coronary artery, *LCA* left coronary artery. (Baird et al. 2021 (Figure 1))

Conclusions

Anesthetic risk and management vary widely based on the age of the presentation, associated abnormalities, and planned intervention in children with congenital aortic stenosis. Critical features to assess include the severity of aortic stenosis, the presence of decreased left ventricular function, and any accompanying hypoplasia of left-sided structures. Identifying high-risk patients is critical as pre-procedural planning and discussion in this subset can mitigate adverse events and optimize outcomes.

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Anomalies of the Aortic Arch, Aortic Coarctation, Interrupted Aortic Arch, and Vascular Rings

Ali Dabbagh and Sri O. Rao

Abstract

Coarctation of the Aorta (CoA) or Aortic Coarctation is one of the most common types of congenital heart disease with a prevalence of 1 in 2500 births, consisting of 5–8% of all congenital heart defects. Some cardiovascular abnormalities are associated with CoA. Anesthesia for coarctation of the aorta mandates an appropriate understanding of the pathology and embryology of the disease. Two different mechanisms have been proposed: the "hemodynamic theory or flow theory" and the "ductal theory or ductus tissue theory." The clinical features include a wide range pending on the age of disease presentation: the prenatal (fetal), the neonatal, infancy, childhood and adolescence, and adult periods. The main treatment approaches include surgical correction, balloon angioplasty (or balloon dilatation), and stent dilatation. Preoperative, intraoperative, and postoperative periods mandate sophisticated anesthesia care. Other pathologies of the aorta and aortic arch including Williams Syndrome, Kommerell's diverticulum, and the Interrupted Aortic Arch are among the other pathologies discussed in this chapter.

Keywords

Coarctation of the aorta · Williams syndrome Kommerell's diverticulum · Interrupted aortic arch · Vascular ring · Congenital heart disease · Anesthesia

Coarctation of Aorta

Introduction and Background

Coarctation of the Aorta (CoA) or Aortic Coarctation is one of the most common types of congenital heart disease presenting itself as an obstructive lesion most often in the thoracic aorta mainly due to narrowing of the aortic isthmus or impaired development of the aortic arch (Foulds et al. 2017). Its prevalence is 1 in 2500 births, consisting of 5–8% of all congenital heart defects and often, some cardiovascular abnormalities are associated with CoA. The disease is much more frequent in males than females. The frequency of CoA is higher in some disease states like Turner Syndrome: 15–20% of CoA cases are Turner's syndrome patients (Torok et al. 2015; Diz et al. 2021).

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CoA is usually being known as a "***discrete narrowing***" of the aorta located at the junction of the ductus arteriosus with the aortic body; this point is just distal to the origin of the left subclavian artery, hence the term "juxtaductal" type CoA is used for it; however, other anatomical sites for CoA are possible and CoA could affect other locations on the aorta in a highly variable manner.

Historically, CoA was regarded "just" as a local anatomical "*narrowing*" in the aortic isthmus which could be *cured and healed with a surgical procedure*; however, this is just an oversimplification. It is the clinical presentation of a broader embryologic impairment and part of a larger and more diffuse systemic disease often involving multiple left-sided cardiac structures; this is discussed more under "embryologic features of the disease" in the later paragraphs.

Being part of a diffuse vasculopathy, CoA may not be resolved even after complete surgical resection of the stricture, mandating life-long follow-up and continuous surveillance; however, some more challenging issues affect the fate of the disease and our clinical practice:

- A*bicuspid aortic valve* is seen in up to 80% of all CoA patients; male dominance is seen both in CoA and bicuspid aortic valve; as mentioned, the bicuspid aortic valve is the most common associated cardiac anomaly, with up to 80% of patients (Keshavarz-Motamed et al. 2013; Lim et al. 2020).
- In a study by Lim et al., it was demonstrated that in adult patients undergoing surgery with the *bicuspid aortic valve*, preexisting CoA leads to younger age for aortic valve surgery and a higher rate of reoperation for aortic insufficiency (Lim et al. 2020).
- Intracerebral Berry aneurysm is the most common ***non-cardiac*** anomaly (10% of patients); both are in favor of an "*underlying disease of the arterial system*"; possibly due to impairment of the neural crest tissue with a resulting "*medial degeneration, aortic root disease, and cerebral aneurysm*" (Campbell 1970; Russell et al. 1991; Matsui et al. 2008; Kim et al. 2020; Levy et al. 2021).
- The anatomical and pathological features of CoA determine the existence or absence of "hypoplastic aortic arch"; the nature of the disease being "simple CoA" or "mixed CoA" having concomitant associated cardiac abnormalities (e.g., ventricular septal defect, bicuspid aortic valve, subaortic stenosis, complex congenital heart defects, and other types of left-sided cardiac lesions) (Santoro et al. 2021).
- Treatment and prognosis depend on the clinical state of the disease: age, a clinical feature of the disease, associated anomalies, "*simple CoA*" or "*mixed CoA*," concomitant arch hypoplasia, hypertension, cerebral vascular involvement, etc. (Kenny and Hijazi 2011; Alkashkari et al. 2019; Agasthi et al. 2020).
- Prenatal and intra-uterine diagnostic approaches for CoA are difficult and imprecise due to the presence of a large fetal patent ductus arteriosus (Familiari et al. 2017; Fricke et al. 2021); however, novel approaches using fetal cardiac magnetic resonance imaging have more accurate results (Lloyd et al. 2021).
- Meanwhile, serial echocardiography should be done after birth in patients with suspicious clinical findings to quickly treat cases of CoA and other obstructive left-heart lesions (Matsui et al. 2008; Adriaanse et al. 2016; Araujo Júnior et al. 2018; Vigneswaran et al. 2020).
- Anesthesia for coarctation of the aorta mandates an appropriate understanding of the pathology, which is more than simply a local narrowing, instead, a global review considering the pathology of left obstructive heart lesions should be kept in mind; however, arteriopathy accompanied with the possibility of left-sided heart disease in the younger patients and the extent of the distal collaterals in the older ones are among the main concerns; some cases are redo patients and one should always care for perioperative treatment of hypertension and extra-cardiac comorbidities (Fox et al. 2019).

Embryology and Anatomic Features

The role of embryological mal-development leading to CoA clarifies the associated anomalies of the disease. Embryological neural crest cells constitute the main origin of many cardiac and non-cardiac structures (Kloesel et al. 2016; Mantri et al. 2021):

- The heart
- Outflow tracts of the heart
- Great vessels including the arch of the aorta
- Conotruncal structures
- The outflow endocardial cushions which are the precursors of the semilunar valves)

Impaired development of the neural crest could lead to some congenital anomalies, both cardiac and non-cardiac; the following are the main cardiac defects related to impaired development of the neural crest (Keyte and Hutson 2012; Gittenberger-de Groot et al. 2020; Mantri et al. 2021; Rosen and Bordoni 2021):

- CoA
- Bicuspid aortic valve
- Hypoplasia of the mitral valve
- Anomalies of the conotruncal structures
- Hypoplasia of the left ventricle
- Anomalies of the cardiac outflow tract (including hypoplasia of the left outflow tract)
- Interrupted aortic arch and hypoplasia of the aortic arch

However, these are the main non-cardiac disorders associated with impaired development of the neural crest:

- DiGeorge Syndrome
- Head and neck anomalies (which could lead to difficult intubation)
- CNS developmental delay

Development involves the third, fourth, and sixth pharyngeal crests as well as the neural crest disorders; however, this process is part of greater embryologic interactions leading to the development of the heart, great vessels, head and neck structures; the entire process of organogenesis highly dependent on the appropriate migration of the neural crest cells; a detailed discussion on embryology of the disease is presented in chapter "Cardiovascular System Embryology and Development" (Gittenberger-de Groot et al. 2020; Mantri et al. 2021).

Etiology and Mechanism of the Disease

Having a better understanding of the underlying causes and mechanisms of CoA could improve the quality of our therapeutic approaches. This is why knowing the correct etiologic mechanisms of the disease has a great effect on clinical outcomes; e.g., why the result of balloon dilatation or imperfect resection of the isthmal strictures increases the likelihood of recurrence of CoA (Jimenez et al. 1999).

There are two main potential etiologies proposed as the causative mechanism for CoA; namely "*ductal* theory or *ductus tissue* theory" and "*hemodynamic* theory or *flow* theory"; described as follows (Krediet 1965; Hutchins 1971; Rudolph et al. 1972; Alkashkari et al. 2019; Agasthi et al. 2020; Kim et al. 2020; Lloyd et al. 2021):

- *Hemodynamic* theory or *flow* theory: More widely accepted, this theory states that during the fetal period, the development of the aortic arch (including the length and the diameter of the arch) depends on "*the amount of blood flow which passes through the arch*"; if this blood flow is impaired (regardless of the underlying pathology) its unwanted effect on the normal development of the aortic arch leads to a narrowed and/or hypoplastic aortic arch; known as "***Rudolph theory***," this phenomenon explains the following main features of CoA: (1) the "*posterior shelf*" which is the characteristic and localized lesion of CoA; (2) the "*intra-cardiac defects*" seen as concomi-

tant embryologic lesions in CoA and an explanation of associated intra-cardiac pathologies decreasing blood flow from the left-heart to the arch of aorta are among the most important etiologies of CoA; (3) "*tubular hypoplasia*" as a distinct but often concomitant lesion of CoA usually seen as narrowing of the aortic isthmus; (4) the right-sided obstructive lesions are very rarely associated with CoA possibly because of increased flow shift from the left-heart structures to right-heart structures.

- *Ductal* theory or *ductus tissue* theory: This theory is also known as the "***Skodaic hypothesis***"; in this theory, it is assumed that "abnormal distribution or aberrant migration" of Smooth Muscle Cells (SMC) from ductus arteriosus to the adjacent aortic tissue leads to CoA; i.e., ectopic ductal tissue in the aortic isthmus causes CoA, which in turn causes constriction, usually in the isthmus of the aorta (i.e., the junction of the aorta with ductus arteriosus); this theory justifies why most cases of CoA are juxtaductal type; though some major controversies exist regarding this theory, there are still some clinicians and embryologists who are "*enthusiasts*" of this theory; those who believe in this theory attribute the cellular and structural similarity between intimal function in CoA and the process of "ductus arteriosus closure" occurring after birth preceded by aggregation of smooth muscle cells in the intimal layer of the aorta at the site of CoA.

Pathologic Findings

The main pathologic finding being the *hallmark of CoA* is the "posterior infolding" or "posterior shelf" of the aortic wall just opposite the site of ductus arteriosus attachment to the aorta; some authors have used the term "*curtain lesion*" to describe CoA. Usually, CoA is located posterolaterally and the ductus arteriosus is located on the anteromedial part of the aortic segment; both being on the same anatomic plane, this pattern is known as juxtaductal CoA; though it is not always the only anatomical presentation of the disease. CoA is usually never seen with pulmonary atresia or pulmonary stenosis while obstructive lesions of the aorta are a common feature seen in association with CoA. The anatomic relationships between typical CoA and the adjacent vascular structures are presented in Fig. 1. Sometimes even circumferential CoA involving the whole lumen of the aorta is possible. Regarding the pattern of involvement in the lumen of the aorta, usually, CoA has a discrete pattern, though tortuous or segmented CoA is possible. CoA usually involves the aortic media, presenting itself as cystic medial necrosis which is the dominant pathologic feature of the disease; however, at times, cystic medial necrosis implicates the whole aortic lumen as an "entire circumferential lesion" with remnants of the ductus arteriosus found in the coarctation tissue. This would imply that there is the presence of ductal tissue; however, the main pathologic features of the aortic tissue are categorized as "*cystic medial necrosis*" accompanied by *hyperplastic intimal thickening*. Then there is intimal *proliferation and disruption of elastic tissues* that occurs after the isthmus of CoA. Some authors believe that cystic medial necrosis associated with intimal proliferation and disruption of elastic tissues is the main pathologic feature responsible for post-balloon angioplasty aneurysm formation in CoA patients. On the other hand, it is hypothesized that the arterial tree is more rigid in the pre-coarctation segment than in the post-coarctation segment. The baroreceptors in the pre-coarctation area are affected due to pre-coarctation hypertension, a finding consistent with postoperative hypertension seen both early and late in repaired CoA patients. There are some pathologic features in common between CoA and congenital aortic stenosis. The pathologic findings seen in CoA include the elastic properties of the aortic tissue which are not entirely resolved even years after surgeries with excellent results but are not limited to a finite region of the aorta; as a matter of fact, surgical repair of CoA does not resolve the underlying "inborn" pathology of "aortopathy"; "impaired elastic property of the vascular sys-

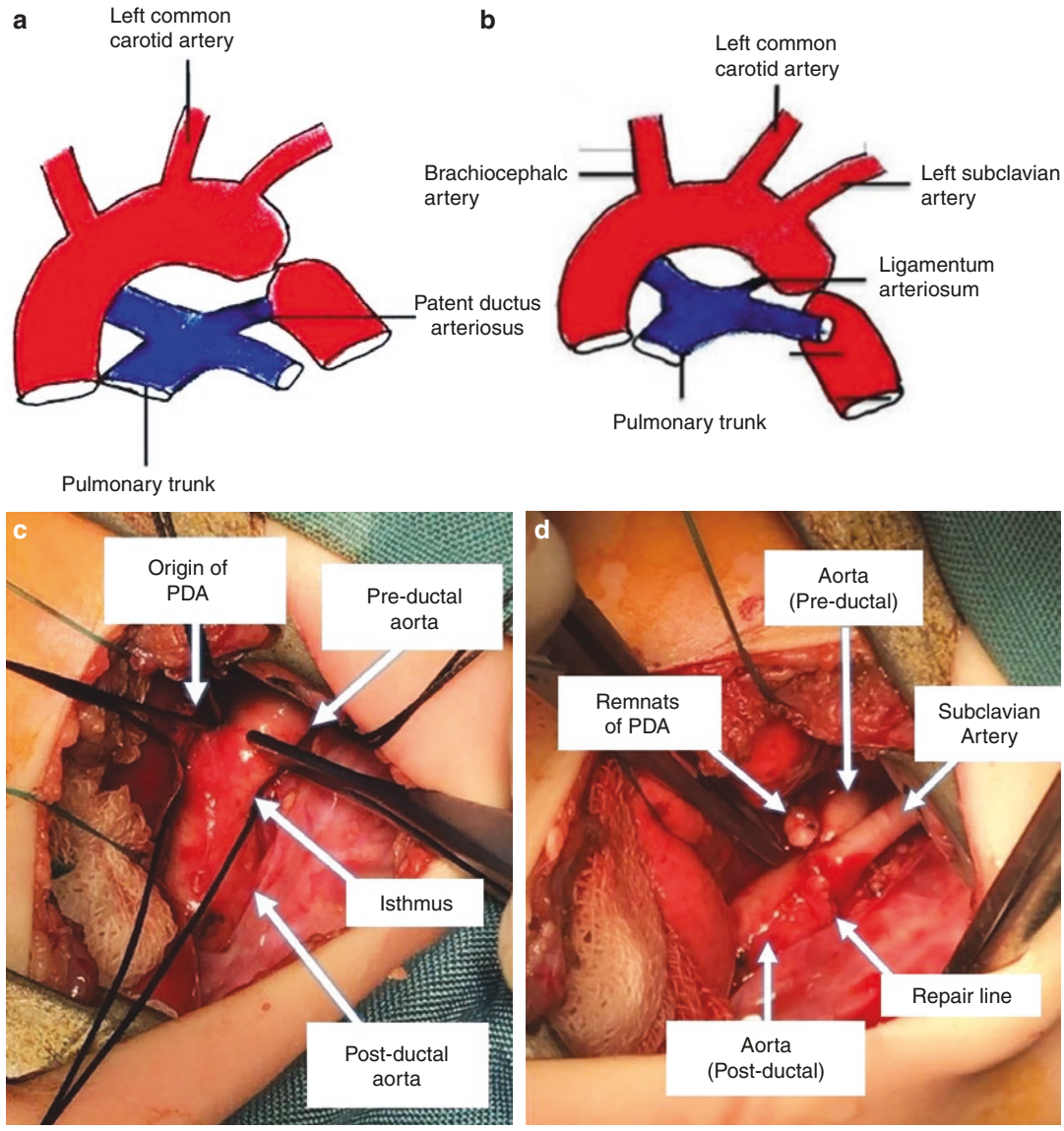

Fig. 1 Coarctation of the aorta; (**a**) Preductal type; (**b**) Postductal type; (**c**) Ductal type before repair; (**d**) Ductal type after repair

tem" is the main reason which could contribute to ***hypertension*** even after treatment. This in turn causes increased load on the left ventricle leading to increased left ventricular mass, systolic and/or diastolic dysfunction of the left ventricle, and finally, their related morbidities. Others believe that widespread vasculopathy seen in CoA patients is primarily the effect of abnormal hemodynamic status due to isthmus narrowing of CoA which is nearly totally resolved after correction of the stricture (Hutchins 1971; Ho and Anderson 1979; Sehested et al. 1982; van Meurs-Van and Krediet 1982; Elzenga et al. 1986; Isner et al. 1987; van Son et al. 1993; Xu et al. 2000; de Divitiis et al. 2001, 2003, 2005; Vogt et al. 2005; Kuhn et al. 2009; Kenny and Hijazi 2011; Pedersen 2012; Niwa 2013; Lee and d'Udekem 2014; Kim et al. 2020).

Clinical Features

In the current era, we could not consider CoA simply as a mechanical stricture of the aorta, which could be relieved by surgery or alternative interventional procedures in the catheterization lab. Neither the natural life span nor the normal hemodynamic status is entirely gained even after complete and successful resection/removal of CoA. Up to 20% of patients have arterial hypertension (usually systolic), arterial atherosclerosis, premature coronary artery disease, heart failure, sudden cardiac death, and unwanted side effects of different methods of CoA repair like post-dilatation aneurysm formation, etc. more than the normal range of the population. However, the age of correction is also among the determinant factors affecting the outcome, though even early correction in the neonatal age does not normalize all clinical findings and "wipe off" all the CoA related clinical features (Pedersen et al. 2011; Pedersen 2012; Vergales et al. 2013; Law and Tivakaran 2021).

The clinical features of CoA are age-dependent; so, we could classify them under 3 main subtitles:

Prenatal Period (Fetal Period)

Prenatal diagnosis of CoA is extremely imprecise even with the most advanced imaging; the following points should be kept in mind to be able to differentiate CoA in the fetal period (Rosenthal 2005; Kenny and Hijazi 2011; Araujo Júnior et al. 2018; Alkashkari et al. 2019; Fox et al. 2019):

- First of all, we should always keep in mind that diagnosis of CoA during the fetal period is somehow a difficult task mandating high levels of suspicion and careful prenatal care; the main reason is that the continuous blood flow through the ductus arteriosus interferes highly with the diagnostic evaluations.
- "***Quantitative hypoplasia of the isthmus and transverse arch***" is the most commonly observed sign in fetal assessment, which could be observed during serial prenatal echocardiography.
- Mixed CoA, which includes the most severe cases of CoA, is associated with "***hypoplasia of the structures of the left heart***" accompanied by stenosis in the aortic isthmus in the fetal period; hence the antenatal diagnosis of severe CoA is much easier in "*mixed CoA,*" while the prenatal diagnosis of "*simple CoA*" is not likely due to the presence of the ductus arteriosus.
- In all CoA patients, whether simple or mixed, prenatal diagnosis of the disease may lead to "*improved survival and preoperative clinical condition.*"
- Within the fetal period, CoA is a significant diagnostic challenge; though hypoplastic left heart should always be considered as a differential diagnosis during fetal echocardiography studies, milder grades of CoA would often reveal a "***near normal***" pattern of fetal echocardiography, especially in late pregnancy which makes the differentiation between "normal right heart structures" and "CoA-associated right heart findings" diagnostic challenges in fetal echocardiography, mandating sophisticated attention regarding potential false positive or false negative results.

During antenatal assessments, we should always consider the potential chance for hypoplasia of left heart structures accompanied by stenosis in the aortic isthmus in the fetal period, mandating serial assessments, especially using sequential echocardiography (Rosenthal 2005; Matsui et al. 2008; Kenny and Hijazi 2011; Alkashkari et al. 2019; Kim et al. 2020):

- First arch Z scores
- Serial isthmal Z scores (in suspected cases with normal outcomes this score improved to >−2; however, this score remained <−2 in those requiring surveillance or surgery)
- Isthmal to ductal diameter ratio
- Isthmal flow disturbance
- Presence of a coarctation shelf
- Hypoplastic aortic arch or interrupted aorta
- Decreased flow through the ascending aorta
- Dilation of the right ventricle and pulmonary artery

Some of the above echo findings are more easily diagnosed during early pregnancy, especially when performed as serial Z scores; while in late pregnancy, the diagnosis is much more difficult mandating serial assessments, especially using sequential echocardiography.

Neonatal Period

The clinical presentation of the neonates with CoA includes the signs and symptoms of low cardiac output; if CoA is a severe type lesion and especially when superimposed by the closure of ductus arteriosus, clinical presentation of shock could be seen; these patients would be diagnosed as critical neonatal CoA due to a severe juxtaductal CoA, clinically presenting with ***different features of heart failure*** as the following findings (Kenny and Hijazi 2011; Alkashkari et al. 2019; Fox et al. 2019; Kim et al. 2020):

- Increased left ventricular filling pressure
- Increased right ventricular filling pressure (i.e., persisting the fetal right heart circulation with high pressure)
- Cardiomegaly
- Impaired left ventricle emptying
- Tachypnea
- Pulmonary edema
- Respiratory distress
- Cardiogenic shock
- Ischemia distal to aortic narrowing leading to organ injury (end-organ ischemia in the liver, kidney, GI tract, etc.)
- Diminished or weak distal pulses including femoral artery

Infancy Period

If the infant with CoA passes the critical neonatal CoA (i.e., the ductus is not closed and the patients receive appropriate medical treatment), the collateral flow may begin to develop; however, during later infancy, ***nonspecific features*** of failure to thrive could be the predominant clinical feature along with cachexia and poor feeding. In almost all situations, weak lower limb pulses could be added to the diagnostic criteria (Rosenthal 2005; Kenny and Hijazi 2011; Alkashkari et al. 2019; Fox et al. 2019).

Older Childhood and Adolescence Period

Often, the more subtle forms of CoA might be undetected until later years of life; however, older children and adolescents with CoA usually present with these findings (Nance et al. 2016; Fox et al. 2019; Law and Tivakaran 2021):

- Hypertension
- Headache
- Claudication of the lower limb
- Exercise intolerance which could be at times the only clinical feature of the disease
- Weak femoral pulses
- The blood pressure gradient between upper and lower limbs

If adequate collateral vessels form during the early years, the above signs and symptoms could be very subtle and the only remaining feature would be increased blood pressure in the upper extremity which is 2 standard deviations above the normal limit for sex and age accompanied by delayed femoral pulsed compared with proximal arterial sites. Also, increased blood flow through the intercostal arteries as the main collaterals would affect the rib margins and result in a typical feature in chest X-rays referred to as "rib notching." Another diagnostic characteristic in chest X-ray is the border of the constricted aorta in the isthmal aortic region called the "reverse 3 sign"; it is clear that "rib notching" on CXR is the result of increased intercostal artery flow so would not be seen in neonates and younger children. These findings are seen in older children and adults and confirmed by transthoracic echocardiography (TTE), CT scanning, MR imaging, MR angiography (MRA), and aortic angiography. Detailed imaging before surgical or catheter-based intervention is mandatory (Nance et al. 2016; Alkashkari et al. 2019; Law and Tivakaran 2021; Lloyd et al. 2021).

Adult Features

If CoA is not diagnosed during the infancy period, the ductus would be closed over time and the aorta would become enlarged enough to produce the large-sized aortic segment, typical of adulthood CoA. However, this underlying pathology, if undi-

agnosed and untreated, more than 80% of patients die before the age of 50. Other associated anomalies seen in adult CoA could be somewhat similar to the lower age range; including the presence of BAV or very rarely left-sided obstructive lesions. Currently, the adult CoA patient populations are comprised of those who have undergone surgical repair, balloon angioplasty, stenting, or a combination of the three methods, with or without residual recurrence of CoA. However, even in those without residual CoA, the clinician should always be aware of the possibility of cardiovascular problems including but not limited to the following (Kenny and Hijazi 2011; Nance et al. 2016; Alkashkari et al. 2019; Lim et al. 2020):

- Arterial hypertension (usually systolic)
- Systemic arterial atherosclerosis
- Premature coronary artery disease
- Exercise intolerance
- Sudden cardiac death
- Stroke
- Heart failure
- Unwanted side effects of different methods of CoA repair like postdilatation aneurysm formation
- Associated anomalies (discussed in the next section)

Echocardiography in CoA

When assessing CoA by echo, the assessment should include complete evaluation throughout the course of the aorta starting from the anatomic left ventricular outflow tract and ending in the descending thoracic aorta, in such a way that any comorbid defects would be diagnosed (Marelli et al. 1993; Aboulhosn and Child 2015; Kim et al. 2020).

The common finding of CoA in echocardiography is narrowing of the aortic arch including 2-D assessments, as well as the pressure gradient>3 mmHg by Doppler flow velocity. When measuring the pressure gradient across the aortic arch, Doppler flow velocity before the point of coarctation should be measured; otherwise, the pressure difference would be exaggerated during the calculation of the pressure gradient. Normally, flow in the descending aorta has a rapid upstroke in systole and brief retrograde flow in early diastole while in coarctation the systolic upstroke is reduced with the continuous forward flow in diastole. In neonatal CoA, an aortic arch measurement less than 4 mm will produce such a gradient as defined by the pressure gradient of CoA.

Echocardiographic Views Used in CoA

In transthoracic echo (TTE), apical two-chamber is used for assessment of descending thoracic aorta, suprasternal view for assessment of the arch, plus descending aorta and thoracic aorta, and finally, subcostal view for abdominal aorta; however, in TEE, the standard exam with emphasis on views demonstrating left ventricular outflow tract and the course of aorta until diaphragm should be used (Aboulhosn and Child 2006, 2015; Upadhyaya et al. 2021).

Echo Protocol

In preoperative assessment, the following comments should be assessed:

- Descending the aorta through Pulsed Doppler at the level of the diaphragm.
- Aortic arch.
- Aortic arch sides and their branching.
- Ascending arch, transverse arch, isthmus, and descending aorta, with special consideration for size and gradient.
- Left subclavian artery.
- Any potential PDA should be searched carefully.
- The left ventricle, regarding its size and function.
- Left atrial size.
- Left-sided obstructive lesions.
- Ruling out regurgitation at any of the four main valves (aortic, mitral, pulmonary, and tricuspid).
- Right ventricle systolic function.
- Pulmonary artery pressure.

Also, in postoperative assessment, the following comments should be assessed (or re-assessed):

- Descending aorta (pulsed Doppler at the level of diaphragm)
- Aortic arch throughout its course
- Ascending arch, transverse arch, isthmus, and descending aorta (size and gradient)
- Any residual PDA
- The left ventricle, regarding its size and function, and the effects of repair on it
- Left-sided obstructive lesions (re-assessment)
- Ruling out regurgitation at any of the four main valves (aortic, mitral, pulmonary, and tricuspid; re-assessment)
- Right ventricle systolic function (re-assessment)
- Pulmonary artery pressure (re-assessment)

Associated Anomalies of CoA

Several reports regarding some cardiac and non-cardiac CoA-associated anomalies have been published half a century ago (Becker et al. 1970; de Swiet et al. 1974; Shinebourne and Elseed 1974); some are discussed here (Agasthi et al. 2020).

Associated Cardiac Anomalies of CoA

Shinebourne reported in 1974 that among 162 patients with CoA, 83 had an intra-cardiac anomaly "resulting in increased blood flow" and 21 had "left-sided lesions present from birth"; while none had "diminished blood flow or right-sided obstructive lesions"; a considerable number of complementary studies were published afterward; based on them, ***cardiac anomalies*** associated with CoA could be classified as the following.

Aortic Valve Lesions

Different aortic valve lesions have been reported to accompany CoA (Perloff 2010; Keshavarz-Motamed et al. 2011; Keshavarz-Motamed and Kadem 2011; Lim et al. 2020):

- Bicuspid aortic valve (BAV)
- Aortic valve stenosis
- Discrete sub-aortic stenosis
- Valve atresia
- Valve obstruction

However, BAV has been reported as the most common aortic valve lesion in CoA patients, being prevalent in 40–80% of the patients with CoA; the proposed mechanism of the bicuspid aortic valve is possibly the embryological etiology of CoA; i.e., mal-development of the neural crest which is the embryologic origin of all these structures, discussed earlier in this chapter; interestingly, BAV is not just another "obstructive lesion" added to the primary CoA lesion; instead it *significantly* affects the following aspects of CoA:

- The severity of the primary pathology
- The harshness of the shearing forces in the aortic lumen
- The magnitude of the eccentric jet in the aortic lumen
- Turbulent flow inside the lumen
- Left ventricle (LV) workload
- The seriousness of the clinical presentation of the disease
- Clinical outcome of the disease
- Final post-surgical outcome

Hypoplasia of the Left Heart Structures

Hypoplasia of the left heart structures could be seen in the most severe forms of CoA; however, hypoplasia of the right heart structures is not a common associated anomaly of CoA. Within the fetal period, CoA is a real challenge in diagnosis; hypoplastic left heart should always be considered as a differential diagnosis during fetal echocardiography studies. Also, other possible left heart obstructive lesions may be seen such as mitral atresia (Hutchins 1971; Shinebourne and Elseed 1974; Sharland et al. 1994; Agnoleti et al. 1999; Connolly et al. 2003; Axt-Fliedner et al. 2009; Stressig et al. 2011; Curtis et al. 2012; Hartge et al. 2012; Cook et al. 2013).

Hypoplasia of the Aortic Arch

In the setting of CoA, hypoplasia of the aortic arch could be classified as one of these three:

- ***Proximal arch segment***: Located just after the ascending arch of the aorta, this segment involves part of the aorta in the distance between the innominate artery and left common carotid artery; this segment should be ≥60% of the diameter of the ascending aorta, otherwise is considered hypoplastic.
- ***Distal arch segment***: This segment is between the left common carotid and left subclavian arteries and should be ≥50% of the diameter of the ascending aorta to be non-stenotic.
- ***Isthmic segment***: This is the third segment of the aortic arch and is located between the left subclavian and the ligamentum arteriosum; it should be ≥40% of the diameter of the ascending aorta, otherwise considered stenotic (Morrow et al. 1986; Kaine et al. 1996; Van Son et al. 1997; Dodge-Khatami et al. 2005; Celik et al. 2006; Alkashkari et al. 2019).

Ventricular Septal Defect (VSD)

Based on a large multi-institutional study, in CoA classification, roughly 30% are simple CoA, 30% are associated with VSD, and 40% are categorized under "complex CoA" lesions; often VSD in CoA patients are conotruncal (Quaegebeur et al. 1994; Glen et al. 2004; Kanter 2007; Kenny and Hijazi 2011; Alkashkari et al. 2019).

Patent Ductus Arteriosus (PDA)

In CoA patients, ductus arteriosus may be the only patent passage for blood flow to the distal parts of the body after the aortic isthmus; so, it is not uncommon to have a PDA with CoA, even it is possible to start intravenous prostaglandin infusion (PGE1) to prevent distal ischemia and to maintain ductal patency; interestingly, PGE1 could also relieve some degrees of narrowing at the coarctation site, besides keeping ductus patent through widening of coarctation area (Liberman et al. 2004; Rosenthal 2005; Carroll et al. 2006).

Atrial Septal Defect (ASD)

The increased pressure in ascending aorta is transferred back to the left ventricle and then the left atrium to keep the foramen ovale open and impose a secundum-type ASD for CoA patients; however, this is very common (Rosenthal 2005).

Bovine Aortic Arch

The right-ward deviation of the left common carotid artery to merge with the brachiocephalic trunk and form a large arterial trunk (bovine trunk) may be seen in CoA (Van Son et al. 1997; Arnáiz-García et al. 2014).

Other Cardiac Anomalies

The other possible defects associated with CoA are (rarely) pulmonary stenosis, anomalous pulmonary venous drainage, persistent left superior vena cava (persistent LSVC) which could affect the normal flow to and from the left ventricle, ductus venous persistence which would create a blood flow to the right heart and atrioventricular canal. As previously mentioned, right-sided obstructive lesions are usually not a common finding with CoA.

Associated Non-cardiac Anomalies of CoA

CNS

In patients with CoA, intracerebral aneurysms are 5 times more common likely especially in those patients between 30 and 50 years old. It is recommended that these patients have assessments of the cerebral vessels by computed tomography angiography (CTA) or magnetic resonance imaging as a routine practice.

Gastrointestinal System

Atresia of the esophagus, tracheoesophageal fistula, diaphragmatic hernia, and atresia of the anorectal area are the main GI co-findings in CoA (Paladini et al. 2004).

Urogenital System

Variant degrees of agenesis or hypo-genesis in kidneys or the urinary tract may be seen in CoA as associated anomalies.

Table 1 Associated anomalies in coarctation of aorta

Associated cardiac anomalies
• *Aortic valve lesions*: Bicuspid aortic valve (BAV); aortic valve stenosis; discrete sub-aortic stenosis; valve atresia; valve obstruction
• *Hypoplasia of the left heart structures*: Hypoplastic left heart syndrome, mitral stenosis
• *Hypoplasia of aortic arch*: Proximal arch segment hypoplasia; distal arch segment hypoplasia; isthmic segment hypoplasia
• *Ventricular septal defect (VSD)*
• *Patent ductus arteriosus (PDA)*
• *Atrial septal defect (ASD)*
• *Bovine aortic arch*
• *Other cardiac anomalies* pulmonary stenosis, anomalous pulmonary venous drainage, persistent LSVC, persistent ductus venosus, atrioventricular canal defect
Associated non-cardiac anomalies
• *CNS*
• *GI tract*
• *Urogenital system*
• *Skeletal anomalies*
• *Chromosomal anomalies*: *Turner syndrome; Shone syndrome; PHACE syndrome; Kabuki syndrome;* Ehler–Danlos syndrome; Marfan syndrome; Loeyz–Dietz syndrome; monosomy X; trisomy 21; trisomy 18

Skeletal Anomalies

Club foot, osteogenesis imperfecta, and some other skeletal anomalies in the lower limb are seen in CoApatients (Smith et al. 1995; Paladini et al. 2004; Lee et al. 2012b) (Table 1).

Chromosomal Anomalies

Chromosomal Anomalies (Shone et al. 1963; Hughes and Davies 1994; Digilio et al. 2001, 2017; Gravholt 2002; Paladini et al. 2004; Kataoka et al. 2006; McMahon and Reardon 2006; Dulac et al. 2008; Perloff 2010; Puttgen and Lin 2010; Schimke et al. 2013; Yuan 2013; Imada et al. 2014; Gorito et al. 2021)

- *Turner Syndrome*: Up to 15% of patients are reported to have Turner syndrome.
- *Shone syndrome:* First described by Shone in 1963, this rare congenital complex is composed of 4 left heart obstructive lesions: "parachute mitral valve, supravalvular mitral ring, subaortic stenosis, and CoA."
- *PHACE syndrome*: ***P***osterior fossa malformation, ***H***emangioma, ***A***rterial anomalies, ***C***oarctation of the aorta, ***E***ye abnormalities; also, there is a newer modification: PHACE(S) to code for ***S***ternal clefting and ***S***upraumbilical raphe; during surgery for correction of CoA, these patents are at increased risk of CNS events and should be monitored carefully.
- *Kabuki Syndrome:* Multiple congenital anomalies including developmental delay, cleft palate, facial appearance of the patient, skeletal malformations, and congenital cardiac defects are the main specifications of this genetic syndrome; most common congenital heart defects in these patients are left-sided obstructive lesions; however, 25–30% of these patients have CoA.
- Ehler–Danlos syndrome.
- Marfan syndrome.
- Loeys–Dietz syndrome.
- Monosomy X.
- Trisomy 21.
- Trisomy 18.

Urogenital System

Variant degrees of agenesis or hypo-genesis in kidneys or the urinary tract may be seen in CoA as associated anomalies.

Skeletal Anomalies

Club foot, osteogenesis imperfecta, and some other skeletal anomalies in lower limb have been reported in CoA patients (Smith et al. 1995; Paladini et al. 2004; Lee et al. 2012b; Imada et al. 2014).

Therapeutic Approaches

The main therapeutic approaches considered for the treatment of CoA could be categorized under 3 main classifications; each of them has several sub-modalities based on the practical method:

- *Surgical correction*
- *Balloon angioplasty* or *balloon dilatation*
- *Stent dilatation*

The last two are usually considered ***percutaneous interventions*** (Suarez de Lezo et al. 2005; Akdemir et al. 2010; Eckroth-Bernard et al. 2014; Hijazi and Kenny 2014; Kim et al. 2020; Goldstein and Kreutzer 2021). Currently, surgical treatment is often reserved for patients with complex CoA or arch defects; however, non-complex lesions are treated with different types of catheters or balloon angioplasty. Intervention-based approaches and surgery under 3 months of age are much more associated with the need for more interventions; also, some associated anomalies like the bicuspid aortic valve could increase the chance for reintervention (Padua et al. 2012; Lim et al. 2020; Dijkema et al. 2021).

Surgical Correction

In 1944 "*the first surgical correction of CoA*" was first reported. Often, surgical correction of CoA is performed through a posterolateral thoracotomy and has been regarded for many decades as "the gold standard treatment for CoA." However, in the current era of interventional treatments, there is an ever-growing controversy regarding "*the best treatment for CoA*" with alternative options (mainly interventional methods including balloon dilatation or stenting) becoming much more popular. As catheter and stent technologies have matured, more centers are choosing stenting or balloon angioplasty as the primary choice for treatment of CoA not only in recurrent CoA but in native CoA. In recent years, with the development of covered stents and smaller delivery systems, many centers have reported improved outcomes and fewer long-term complications as compared to surgical cohorts. Despite this, stenting has not yet become the standard first choice and some controversies remain yet. In 2011, *the American Heart Association* released its Scientific Statement:

> "For native coarctation of the aorta, surgical repair (extended resection with an end-to-end anastomosis) remains the gold standard" while "balloon angioplasty with or without stent implantation" is considered as an alternative option with less invasiveness; though it should be kept in mind that "transcatheter treatment *does not necessarily replace* surgical management"

However, The *Cochrane Database* systematic review published in 2012 has declared that "there is insufficient evidence with regard to the best treatment for coarctation of the thoracic aorta" (Mahadevan and Mullen 2004; Forbes et al. 2007a, 2011; Turner and Gaines 2007; Botta et al. 2009; Egan and Holzer 2009; Holzer et al. 2010; Feltes et al. 2011; Padua et al. 2012; Hijazi and Kenny 2014; Sohrabi et al. 2014; Alkashkari et al. 2019).

Some clinical notes should be considered in patients undergoing surgical correction of CoA:

- The majority of "neonatal and infantile CoA cases" are presented as "arch hypoplasia."
- In patients with arch hypoplasia, surgical correction is the first option.
- Usually, *end-to-end anastomosis with extended resection* is the best approach during the first months of life.
- Other surgical approaches for CoA repair include "subclavian flap angioplasty," "patch angioplasty," and "interposition graft repair."
- In surgical correction of CoA, postoperative complications should be followed vigorously, including *re-CoA* (recurrence of stenosis), *aneurysm* formation, persistent *hypertension* (at rest or during exercise), *stroke,* and accelerated *coronary artery disease.*
- Some of these postoperative complications are lethal though they are infrequent (like rupture at the site of surgical repair).

The relatively high rate of postoperative events in CoA patients underscores the pathologic basis of the disease: "*surgical correction of CoA only resects the local anatomical isthmus but not the underlying vascular impairment generating the disease.*"

Though isolated repair of CoA is associated with favorable results, all surgical approaches are associated with a chance of restenosis, i.e., re-CoA (with a rate of about 20–40%); advanced microsurgical techniques accompanied with a vigorous and sophisticated approximation of the two ends of the anastomosis may decrease restenosis rate while weight and age at the time of operation could affect the chance of re-CoA. Fortunately, restenosis is often non-lethal and could be treated by surgical approach or by catheter-based intervention, each of these two methods has its merits and risks (Connors et al. 1975; Backer et al. 1995; Bouchart et al. 2000; Azakie et al. 2005; Suarez de Lezo et al. 2005; Abbruzzese and Aidala 2007; Hijazi and Awad 2008; Kuroczynski et al. 2008; Botta et al. 2009; Vohra et al. 2009; Kische et al. 2010; Feltes et al. 2011; Luijendijk et al. 2012; Pedersen 2012; Alkashkari et al. 2019; Dijkema et al. 2021; Goldstein and Kreutzer 2021).

Balloon Dilatation

For many years, surgical repair of CoA was considered the only available definitive therapy for CoA patients; however, in 1979 Sos et al. collected coarcted segments of the aorta from postmortem specimens and demonstrated the ability to dilate the tissue; this finding was the first step in the application of definitive non-surgical therapies (Sos et al. 1979). Afterward, Singer and colleagues reported successful dilatation of CoA in a 42-day old infant; interestingly, this first case of balloon dilatation was done after unsuccessful surgical repair leading to restenosis (Singer et al. 1982).

Indications for balloon dilation of CoA are the same as surgical repair and include:

1. Systolic pressure gradient before the stenosis of CoA, more than 20 mmHg
2. Severe CoA demonstrated in angiography associated with extensive collaterals

However, based on the current evidence the following could be considered as the main applications of balloon dilatation angioplasty for CoA patients:

- Discrete CoA
- Discrete recurrent CoA
- Restenosis after previous surgical repair of CoA (i.e., ineffective surgical repair)
- Residual coarctation after surgical repair (i.e., ineffective surgical repair)
- Infants above 1 month and below 6 months have discrete narrowing but no evidence of arch hypoplasia
- Native CoA beyond the neonatal period (***controversial***); though some believe the minimum age for balloon dilatation and stenting is 3 months (Abbruzzese and Aidala 2007)

A considerable number of studies have demonstrated balloon dilation angioplasty as a good alternative among the first line of corrective treatments to remove isthmal stricture in discrete CoA, in neonates, adolescents, and adults, with excellent long-term outcomes. Also, the results of balloon dilatation are safe and effective, even years after primary therapy, i.e., during later clinical follow-up. However, other studies have shown that balloon dilatation of CoA causes neointimal proliferation of undifferentiated smooth muscle cells into the aortic lumen, causing restenosis after primary balloon dilatation. One of the issues with balloon dilatation that has been controversial is its application for native CoA, especially when compared with other methods regarding the risk of aneurysm formation. Current evidence has not resolved this controversy (Fawzy et al. 1992, 1997, 1999, 2004, 2008; Takahashi et al. 2000; Hassan et al. 2007a, 2007b; Hijazi and Awad 2008; Rothman et al. 2010; Feltes et al. 2011).

Complications of balloon angioplasty are similar to stent dilatation, discussed more in the next section under "stent dilatation"; they include the following in brief:

- "Aortic disruption" and "aortic dissection"
- Blood leakage
- Injury to the femoral artery and the resulting impaired femoral pulse

- *The most common complication* is aortic aneurysm formation after balloon dilation distal to the site of angioplasty; especially but not limited to native CoA
- Restenosis which may lead to re-CoA (Feltes et al. 2011)

Stenting

Stenting includes transcatheter insertion of stents to implant and dilates the stent at the location of the isthmal stricture; this method has been described for the first time in 1991 with good results and is now considered first-line therapy in most adolescents and adults and those with restenosis. Short-term results of stenting in CoA (i.e., decreasing the gradient across the isthmal stricture) and also, long-term outcomes (especially the incidence of postdilatation aneurysm formation and restenosis) are promising. Improvements in stent technology have decreased the age of stenting to smaller patients to as young as 3 months with these patients requiring multiple redilations to accommodate a growing patient's aorta. The success rate of stenting in CoA patients is more than 95% with an immediate drop in systolic blood pressure gradient and increase in aortic diameter. Stenting for CoA has been compared with both balloon dilatation and surgical repair of CoA. Stenting leads to favorable clinical outcomes regarding relief of hypertension, especially after surgical correction of CoA. Interestingly, some patients with no arm-leg gradient at rest may develop a blood pressure gradient with exercise (the so-called post-treatment exercise-induced hypertension "EIH"); however, CoA patients treated with stenting do not often experience this problem. Also, covered stents have been introduced for CoA patients as safer devices to prevent unwanted complications of bare metal stents including aortic wall trauma, aneurysm formation, and migration of stents; however, the currently available evidence is in favor of equal safety and efficiency of the two types of stents though most experienced operators opt for covered stents in high-risk patients. These include patients including those with underlying aortic aneurysms, patients with nearly occluded aorta and aortic atresia, patients with an age of 40 or more, and patients with Turner syndrome.

The complications of stenting in CoA patients are infrequent, i.e., the chance for acute complications, especially rupture of the aorta is very low (about 2%); while the rate of long-term complications is relatively less than other therapeutic options. The rate of aneurysm formation is 5–10% and the rate of restenosis is about10% or less than that; however, sophisticated care is needed to detect and if necessary, treat any untoward complication; these include:

- "Aortic disruption" and "aortic dissection" can be life-threatening complications mandating aggressive and prompt treatment by the medical team (*immediate*).
- Blood leakage, i.e., blood extravasation at the site of stent implantation (*immediate*).
- Impaired femoral pulses especially when it is due to femoral arterial thrombosis (*immediate*).
- Intimal layer growth and proliferation inside the lumen of the stent which could lead to restenosis, leading to re-CoA, especially at "early age" patients with small-bore stents (*long-term complication*).
- Stent migration or stent mal-positioning.
- *The most common complication* is the occurrence of aortic aneurysm (*long-term complication*); the incidence of aneurysm formation is less than balloon angioplasty alone. Aneurysm formation may occur even after the application of covered stents; aneurysm formation continues to have a persistent risk for all CoA patients; whether they are treated surgically, by balloon dilatation, or by stent dilatation with a mortality rate between <1 and>90%; this wide range shows the very remarkable differences in management and outcome of aortic aneurysms related to CoA-treatment. These patients can often be treated using endovascular stent grafts (Suarez de

Lezo et al. 1999, 2005; Cheatham 2001; Hijazi 2003; Varma et al. 2003; Kothari 2004; Mahadevan and Mullen 2004; Markham et al. 2004; Forbes et al. 2007a, 2007b, 2011; Marcheix et al. 2007; Hijazi and Awad 2008; Botta et al. 2009; Egan and Holzer 2009; Akdemir et al. 2010; De Caro et al. 2010; Holzer et al. 2010; von Kodolitsch et al. 2010; Feltes et al. 2011; Godart 2011; Hormann et al. 2011; Kenny et al. 2011; Kenny and Hijazi 2011; Kannan and Srinivasan 2012; Luijendijk et al. 2012; Padua et al. 2012; Baykan et al. 2014; Khavandi et al. 2013; Ringel et al. 2013; Hijazi and Kenny 2014; Sohrabi et al. 2014; Alkashkari et al. 2019; Dijkema et al. 2021; Goldstein and Kreutzer 2021).

Anesthesia for CoA

Preoperative Evaluation

Preoperative care depends mainly on the age of diagnosis; if the patient is diagnosed in the neonatal or infantile period, the main goal in preoperative care would be to stabilize hemodynamic status, correct the acidotic milieu of the under-perfused organs and improve the underlying failing heart as much as possible; while in adolescent and adult CoA patients, we mainly aim to control blood pressure, especially in the upper trunk and upper extremity.

Preoperative Care in Neonatal and Infantile Period

These should be performed in this group of CoA patients:

- Insert a reliable intravenous line (e.g., central venous line or umbilical vein line).
- Continue intravenous prostaglandin infusion to maintain patency of the ductus arteriosus.
- Keep hemodynamics stable and compensate for underlying heart failure; with the help of inotropes, fluid optimization, and diuretics.
- Assist ventilation whenever the patient is in respiratory failure.
- Start monitoring especially hemodynamic and respiratory monitoring.
- An indwelling arterial line from the right hand is the preferred approach for invasive blood pressure monitoring.

Preoperative Care in Older Children and Adults

- Control of upper trunk hypertension which could be effectively controlled with beta-blockers; however, vigorous treatment and "normalization" of blood pressure in the upper trunk should be avoided to prevent the possibility of post-ductal ischemia.
- Assessment of LV function to check the contractility and the undiagnosed associated cardiac defects.
- Long-term CNS effects of CoA and possible microaneurysms.
- A well-developed network of collaterals to the lower limb and the spinal cord.

Intraoperative Anesthesia Management

Anesthesia Induction and Maintenance

Either intravenous or inhalational anesthesia agents or a combination of them could be used for induction; however, ***extreme caution*** should be exerted to prevent blood pressure drop after induction in patients with the ductal-dependent distal flow. Also, for the maintenance of anesthesia, both intravenous and inhalational agents could be used. The thoracic paravertebral block could have benefited both intraoperative and postoperative analgesia; however, there is always the risk of masking signs of early postoperative paraplegia by the block; the same could be correct for thoracic epidural analgesia (Turkoz et al. 2013; Fox et al. 2019).

Lung ventilation should be kept at normocapnia to prevent potential cerebral vasoconstriction

and reduce the risk of cord ischemia. One lung ventilation management is another challenge for anesthesiologists, especially in very young patients.

Monitoring

Pre-ductal and post-ductal SpO2 and noninvasive BP monitoring should be started at the first stages of patient arrival on the operating room table and should be continued after the installation of invasive arterial blood pressure monitoring; their data are useful especially during the clamping interval. ***Invasive blood pressure monitoring*** through the right arm shows the preductal arterial pressure unless there are abnormal patterns of aortic anatomy or circulation from the aorta to the upper extremities. Distal extremity blood pressure control should be done; if not possible by invasive blood pressure control and if not, at least through a non-invasive blood pressure cuff. A ***Central venous catheter*** helps us both provide fluids and give vasoactive drugs and at the same time, manage the loading status of the patient (Familiari et al. 2017).

CNS Monitoring

There should be close CNS monitoring both for the brain and the spinal cord. One should always keep in mind the possibility of rapid changes in blood pressure, the risk of spinal cord ischemia during aortic clamp especially below 1 year, preexisting CNS vascular abnormalities including congenital anatomic aberrations (in younger patients) or the acquired defects (in older patients) due to chronic head and neck hypertension; all of the stress on the importance of especial attention to CNS monitoring.

Somatosensory and motor evoked potentials (SSEP and MEP)are both sensitive indicators of distal perfusion and could alarm anesthesiologists in case of ischemia distal to the clamp (including the spinal cord).

NIRS has gained important attention during the last decade as monitoring not only for CNS but also, as an indicator for perfusion of other organs; the following are among the main benefits of NIRS monitoring during perioperative care of CoA:

- It is a sensitive, real-time, and non-invasive monitor indicating the oxygenation status of the tissue; NIRS has been demonstrated in many studies to be an important indicator of maintained tissue perfusion; both ***cerebral*** and ***somatic*** assessments of perfusion are useful in these patients (i.e., cerebral rSO2 and renal rSO2).
- Cerebral impairments in CNS perfusion due to blood pressure drops affecting the NIRS number should be treated promptly, especially after induction of anesthesia or after removal of the clamp; also, it may help us avoid hyperventilation inducing cerebral vasoconstriction.
- Using multisite NIRS is especially important when considering the possibility of blood flow manipulations and cord ischemia; besides monitoring CNS O2 content, NIRS could monitor the possibility of ischemia induced by aorta clamping, which would be demonstrated as a decline in NIRS number; especially, when the drop is much more severe than the cerebral NIRS.
- NIRS could let us know whether the collaterals are well developed or not; in neonates and young infants below 1 year, a rapid drop in somatic NIRS usually happens due to violations in blood pressure during the procedure, especially during the clamp, due to less developed collaterals; while in patients older than 1 year, there is not such a great drop in NIRS after clamping mainly due to improved collateral flow (Becker et al. 1970; van Son et al. 1993; Berens et al. 2006; Moerman et al. 2013; Neshat Vahid and Panisello 2014; Scott and Hoffman 2014).

Vasoactive Drugs

One of the most important tasks of an anesthesiologist during CoA operation is the management of blood pressure during clamp manipulations; i.e., ***to control blood pressure during clamp and***

to treat the aftermath of the clamp. For this purpose, during clamp time, "partial" and not "total normalization of blood pressure" is a key component; a moderate degree of hypertension and avoiding vigorous treatment of higher blood pressures during clamp time helps us prevent profound pressure drop after clamp removal; always keep mean arterial pressure (MAP) over 45 mmHg; meanwhile, in older patients, hypertensive episodes during clamp time are really dangerous regarding the risk of vascular events involving CNS arterial system (Imada et al. 2014).

Nitroprusside has an important role: the patients have a major arterial disease, so, there is a need to control the arterial tree response using nitroprusside to control blood pressure; this is of utmost importance during the clamp of the aorta (Gelman 1995).

Nitroglycerin is used as an effective and reliable agent for controlling blood pressure proximal to the clamp; some believe that it is more beneficial than sodium nitroprusside for proximal pressure control (Moerman et al. 2013).

Phenylephrine: When the aorta is repaired and the surgeon wants to remove the clamp, some preventive strategies should be used to overcome the sudden drop in blood pressure including the use of vasoconstrictors like phenylephrine; however, careful and titrated use of vasopressors should always be the practice to prevent abrupt hypertensive spikes.

In older children and adults, usually, long-term upper trunk hypertension is seen in these patients, so, there should be a great concern regarding the prevention of any potential untoward CNS hazards and assessment of possible microaneurysms. However, during aortic clamp in these patients, blood pressure should be balanced in such a way to prevent both increased intracerebral hypertension and also, post-ductal ischemia in the lower limb. Besides, the long-term effect of CoA is associated with a well-developed network of collaterals that perfuse the lower limb and the spinal cord; their role should be regarded as well. Spinal cord protection needs vigilance, taking the time appropriately and with sophisticated care, and prevention of cord ischemia during the surgery; ***careful beat-to-beat monitoring during clamp time*** is the cornerstone of all these strategies.

Spinal Cord Protection Strategies

All surgical attempts should be done to keep ***cross-clamp time*** less than 20 min.

NIRS: This is a sensitive, real-time, and non-invasive useful monitor monitoring the oxygenation status and the possibility of anaerobic metabolism in ischemic tissues.

SSEP and MEP are sensitive monitors for the detection of any potential ischemia in the spinal cord.

Prevention of "overtreatment of blood pressure" and early compensation for any blood pressure drop after clamp removal is necessary for adequate perfusion of the cord.

Prevention of hyperventilation is among the other necessary strategies for the prevention of spinal cord ischemia.

Mild hypothermia (as low as 34–35 degrees of centigrade) could help protect the spinal cord tissue.

The surgeon should ***avoid clamping collaterals*** during the clamp period.

Patient Positioning

Usually, the patients have a left-sided aortic arch which is the common pattern of the aorta; so, the usual position is right lateral decubitus; which is accompanied by the left lung collapsing during surgery; its related considerations should be kept in mind.

A summary of intraoperative anesthesia management for CoA.

Induction of anesthesia	Caution for prevention of blood pressure drop in ductal-dependent patients
Monitoring	1. Pre-ductal and post-ductal SpO2 and noninvasive BP 2. Pre-ductal and if possible post-ductal invasive BP 3. Central venous catheter for monitoring and drug infusion 4. Somatosensory and motor evoked potentials (SSEP and MEP) 5. NIRS
Vasoactive drugs	1. Careful, beat-to-beat monitoring during clamp time avoid vigorous treatment of blood pressure during clamp. 2. Avoid profound blood pressure drop after clamp removal (MAP always >45 mmHg). 3. Nitroprusside, nitroglycerine, and phenylephrine should be used cautiously. 4. In older patients, hypertensive episodes during clamp time are really dangerous for CNS arteries.
Protection of the spinal cord	SSEP and MEP Cross clamp time not to exceed 20 min Avoid profound blood pressure drop after clamp removal Prevention of hyperventilation Mild hypothermia (34–35 degrees of centigrade) The surgeon should avoid clamping collaterals during the clamp period.

Postoperative Care

Several main topics should be considered as the core postoperative care in CoA patients:

- It is mandatory to monitor ***postoperative blood pressure*** vigorously; since the prevalence of this event is considerable after correction of the lesion; postoperative sodium nitroprusside, infusion of beta-blockers like esmolol and ACE inhibitors could be added to fix the problem; the prevalence of postoperative hypertension is especially higher in those with a diagnosis of "small or hypoplastic aortic arch" before the operation (O'Sullivan et al. 2002; Rouine-Rapp et al. 2003; Tabbutt et al. 2008; Lee et al. 2012a; Matisoff et al. 2015; Fox et al. 2019).
- ***Postoperative pain control*** is another main feature that should be considered to effectively control blood pressure.
- Whenever possible, the patients should be extubated at the end of surgery; appropriate postoperative hemodynamic, respiratory, and metabolic conditions are prerequisites for extubation.
- Checking for motor activity in the postoperative period is an essential part of the care that should not be neglected at all; of course, as soon as the patient is awake and gains full muscle force recovery.

Clinical Outcome

In the current era of congenital heart disease, CoA is no longer considered a simple disease, especially when considering that treatment of CoA, with any of the modalities discussed in previous parts, is rarely definitive. Total resolution of the patients is faced with chronic challenges including recurrence (re-CoA) and/or aneurysm. Without treatment, the mortality rate is increased; and the mean age of death in CoA patients is 32–34 years. Also, without treatment, the survival of CoA patients, when calculated from birth time until 58 years, is about 90%; this is why early treatment is essential. Early curative treatment decreases the rate of mortality; while, recurrence of aneurysms despite successful repair remains a major risk factor for death. Finally, CoA is associated with higher mortality and lower outcome in patients with associated anomalies; often this is the case in neonates and younger children who have significant associated morbidities (Shinebourne et al. 1976; Suarez de Lezo et al. 1999; Celermajer and Greaves 2002; von Kodolitsch et al. 2002, 2010; Verheugt et al. 2008; Axt-Fliedner et al. 2009; Lee and d'Udekem 2014; Alkashkari et al. 2019; Fox et al. 2019; Kim et al. 2020; Dijkema et al. 2021; Goldstein and Kreutzer 2021).

Despite the morbidity and mortality, CoA patients have relatively acceptable functional health states and are comparable with the normal population. However, the following points should be considered as comorbidities associated with CoA even after repair:

- Cardiac disease; including decreased cardiac output and also, heart failure presenting as an increased mass of the left ventricle, systolic and/or diastolic dysfunction of the left ventricle
- Hypertension mandating antihypertensive treatment
- Diseases of the aorta and the aortic trunk (including aneurysm formation, ectasia in the ascending aorta, regurgitation of the ascending aorta, etc.)
- Though surgical correction of CoA removes the anatomic narrowing, the underlying vascular disease, and possible vasculopathy remains
- Recurrence of aortic stenosis (i.e., Re-CoA) which is a relatively frequent problem necessitating repetitive intervention(s) including surgical or non-surgical modalities; however, some believe that re-CoA is more frequent in the complex CoA compared with simple CoA patients
- Premature coronary artery disease and/or cerebrovascular disease
- Aneurysm formation: Different studies across different centers have announced very different rates for aneurysm formation after repair of CoA: 1–51%! This could be to some degree due to the diagnostic criteria for aneurysm and diagnostic criteria for the aneurysm. The following could be considered as risk factors for aneurysm formation.
  - Patch graft technique
  - Late repair of CoA
  - High preoperative gradient across CoA
  - Bicuspid aortic valve
  - Inherent properties of the aortic wall (i.e., wall weakness)
- Acute kidney injury (AKI) is among the perioperative problems that might be encountered during the repair of CoA (O'Rourke and Cartmill 1971; Fawzy et al. 1997, 2004, 2008; Celermajer and Greaves 2002; O'Sullivan et al. 2002; von Kodolitsch et al. 2002, 2010; Hassan et al. 2007a; Vohra et al. 2009; Pedersen et al. 2011; Pedersen 2012; Jang et al. 2014; Tong et al. 2014; Fox et al. 2019; Kim et al. 2020; Goldstein and Kreutzer 2021).

Other forms of aortic stenosis

- Supravalvular aortic stenosis is categorized under a group of diseases with some similar properties. Among this classification, Williams Syndrome is just mentioned here; though, a detailed discussion could be found in chapter "Congenital Heart Disease".
- In brief, Williams Syndrome is a syndrome with cardiovascular involvements, a characteristic facial appearance, endocrine, and connective tissue abnormalities, and mild cognitive abnormalities; usually, the aorta has a thick texture due to tissue changes. Stenosis is most severe at the sinotubular junction, being corrected using a "Doty patch" to increase the diameter of the aorta at the sinotubular junction; usually, the incision is done at the point between right and non-coronary sinuses just above the aortic valve (Matisoff et al. 2015; Yuan 2017).
- Kommerell's diverticulum refers to the developmental erroneous aneurysmal dilatation, occurring in the descending aorta, usually as a remnant of the fourth dorsal aortic arch, at the origin of an aberrant subclavian artery (Tanaka et al. 2015; Bhatt et al. 2016). The nomenclature is used after Dr. Kommerell, a German radiologist, 1936, who made the first diagnosis on a living individual. Kommerell's diverticulum may occur both in the right- and left-sided aortic arches (de Campos et al. 2012; Meester et al. 2022). The main pathologic feature is cystic medial necrosis in the diverticulum wall (Tanaka et al. 2015). Both open and hybrid surgical approaches have been tailored pending the underlying anatomy (Dinh et al. 2021; Worhunsky et al. 2021).

Interrupted Aortic Arch (IAA)

IAA is a disease of total aortic absence; and unlike CoA, no remnants of aorta exist; the most common anatomic location for IAA is between the left common carotid and left subclavian.

Two main theories are suggested for IAA:

- Blood flow theory, which considers IAA with malalignment of VSD and sub-aortic stenosis.
- Ductal tissue theory; only in type B of IAA this theory might be proposed; otherwise, in type A, ductal tissue theory is not considered a possibility.

Classification of IAA

The classification of IAA was introduced in 1959 by Celoria and Patton; this classification affects the clinical outcome and also, the surgical procedure (Celoria and Patton 1959; McCrindle et al. 2005). IAA is mainly categorized into three main types (Figs. 2 and 3):

- Type A: The lesion is anatomically located at the isthmus; i.e., near the ductus and before the origin of the left subclavian artery.
- Type B: The lesion is located in the distal arch; i.e., between the origin of the left subclavian and left common carotid arteries; this is ***the most common*** type of IAA; in this type, the absence of a distal arch leads to impalpable pulses in both the left hand and femoral arteries; while the right hand has a palpable pulse. Also, there is a strong association between type B and DiGeorge Syndrome.
- Type C: The lesion is in the proximal arch, i.e., between the origin of innominate and left common carotid arteries; this is an ***extremely rare*** form of IAA.

Associated Anomalies

It has been demonstrated that nearly all neonates with IAA have coexisting congenital heart disease (Patel et al. 2015; Ramirez Alcantara and Mendez 2021):

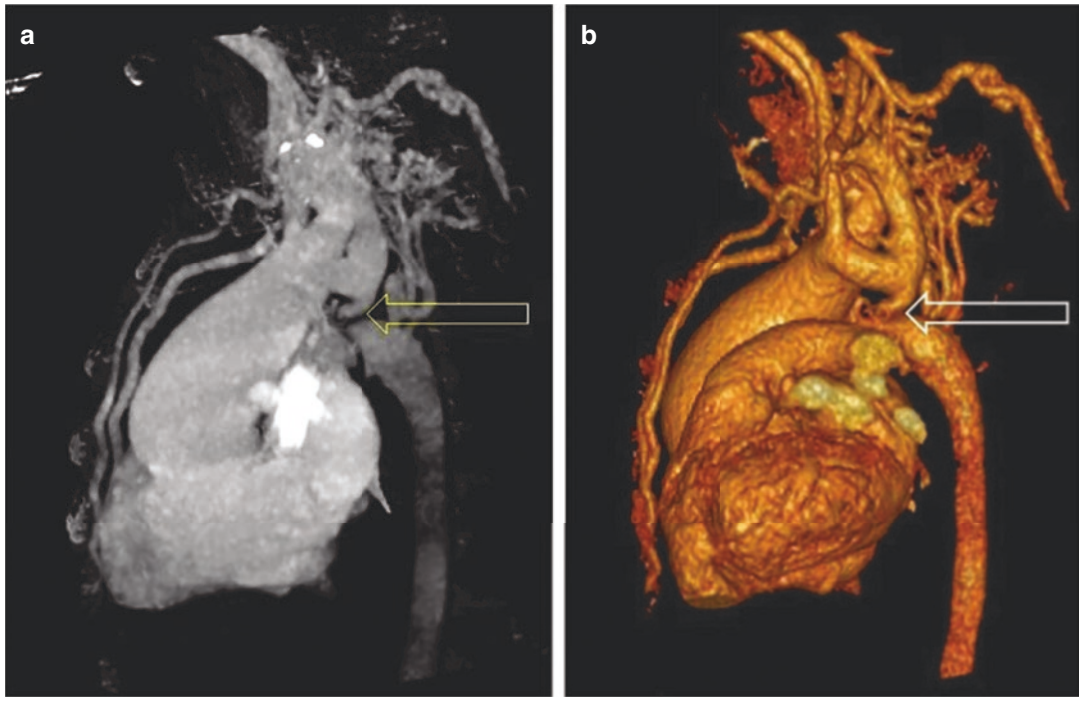

Fig. 2 Type-A Interrupted aortic arch; in both angiography and computer tomographic reconstruction. Note that all head, neck, and upper extremity vessels arise proximal to the ductus arteriosus. Distal blood flow beyond the aortic arch arises from the ductus arteriosus. (**a**) CT angiogram of the lesion (The Arrow shows the site of interruption). (**b**) Computed tomographic reconstruction of the lesion (The Arrow shows the site of interruption)

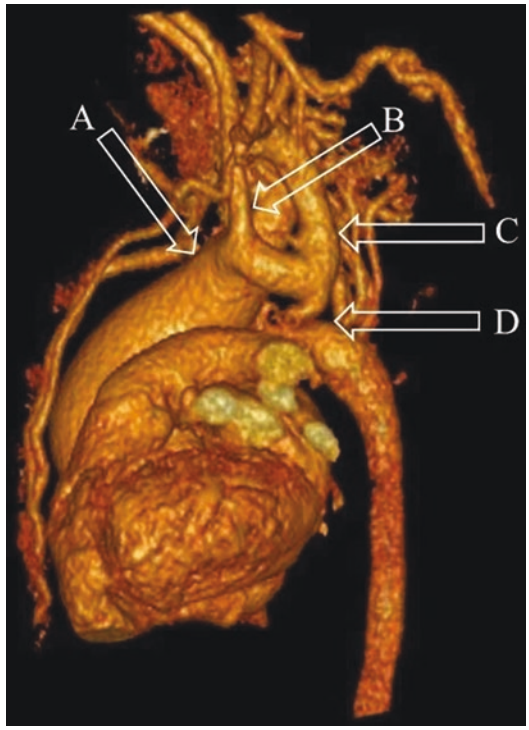

Fig. 3 Vascular components in the computed tomographic reconstruction of the Type-A interrupted aortic arch: (**a**) Proximal aorta (before the lesion). (**b**) Left internal carotid artery. (**c**) Left subclavian artery. (**d**) The location of the interruption

- Ventricular septal defects (the most frequent associated cardiac anomaly)
- Truncus arteriosus
- Aorticopulmonary window
- Patent ductus arteriosus

Clinical Findings

Before birth, the clinical findings of the IAA patient are not critical since the blood flow to the body's organs depends minimally on blood flow through the aorta. Distal blood flow is highly dependent on the patency of ductus arteriosus if IAA is diagnosed during the fetal period, prostaglandin E1 infusion should be started promptly after birth to prevent ductal closure otherwise, severe distal ischemia occurs with the following results:

- Hepatic ischemia leading to increased liver aminotransferases.
- Splanchnic and gut ischemia leading to necrotizing enterocolitis.
- Renal ischemia leading to anuria and severe kidney injury.
- In type B of IAA, there is the risk of ischemia in those parts perfused by the left subclavian artery.
- Finally, distal ischemia leads to injury in all parts of the body and other organs, causing severe myocardial depression and low cardiac output.
- Impaired cerebral perfusion and acidosis lead to a brain seizure.
- In brief, the prognosis of severe distal ischemia and systemic acidosis is poor (Oosterhof et al. 2004; Ramirez Alcantara and Mendez 2021).

Diagnosis: IAA is usually diagnosed using echocardiography. Prenatal echocardiography could be of great help. Often, the majority of the patients need no further assessment including angiography; though in some cases with rare anatomic patterns of disease, MRA (magnetic resonance angiography) may be helpful to detect the lesion and concomitant anomalies much more precisely (Geva et al. 1993; Dillman et al. 2008). However, in echocardiography, the following are among the main items to be examined:

- The anatomic location of interruption (i.e., type of the disease)
- The length of interruption and discontinuity of the aorta
- The diameter of the ascending aorta and the aortic valve
- The narrowest portion of the left ventricular outflow tract (LVOT); an LVOT area is equal to or less than 0.7 cm^2/m^2 has been demonstrated as "a sensitive predictor" of post-repair LVOT obstruction (Geva et al. 1993)
- Other associated anomalies like VSD or ASD
- The size and presence of thymus for the probability of DiGeorge syndrome

The above items are to be compared with post bypass exam findings in intraoperative TEE.

Infusion of intravenous prostaglandin in infants with IAA is an integral component of the treatment; so, in the minority of the cases that such a patient undergoes angiography, hemodynamic assessments are not so practical and/or useful except for the assessment of the LVOT adequacy, which its measurement is not affected by prostaglandin infusion.

Treatment

IAA is a disease needing curative surgery to be treated. Prenatal diagnosis helps diagnose the disease and its types much earlier.

Surgical treatment: The current method for treatment for IAA is the single-stage repair of the aorta using direct anastomosis between ascending and descending aorta. This procedure is done through a median sternotomy and requires appropriate relief of both proximal and distal segments of the aorta before anastomosis. However, staged repair is used in some centers (Brown et al. 2006; Ramirez Alcantara and Mendez 2021).

Although the surgical approach for "native" IAA is considered a curative method, IAA is a chronic disease and subsequent treatments for relief of probable future re-stenosis are often part of the treatment protocol (Jegatheeswaran et al. 2010).

However, for primary surgical relief, usually, hypothermic circulatory arrest cooling to 18 °C is used; however, a growing number of centers use selective antegrade cerebral perfusion for brain protection. Needless to say, neuromonitoring with both NIRS and Transcranial Doppler (TCD), hematocrit levels of 25% or more, pH-stat strategy, and especially, good experience of the surgeon to decrease the time of aortic clamp are the main determinants for good CNS outcome.

Usually, no interventional treatment is considered an option for native IAA unless recurrence of stenosis after primary surgical repair; in some studies, the rate of restenosis needing interventional treatment is low; while some studies have claimed a relatively higher rate of restenosis needing relief of the stenotic site with balloon dilatation. However, as mentioned earlier, IAA is a chronic disease; so, care should be given to detect any restenosis after primary successful surgical repair.

For the surgical operation to be done, sophisticated perioperative care is mandatory which begins with prenatal diagnosis, postpartum stabilization of the newborn using secure and safe intravenous lines, administering intravenous prostaglandin infusion with the restoration of organ perfusion to prevent ischemia and acidosis, acid-base, and respiratory therapy to normalize blood pH and keep PCO2 between 40 and 50 torr, and other measures that are discussed under "anesthetic management."

Anesthetic management: Perioperative care is discussed under 3 subtitles: preoperative, intraoperative, and postoperative period.

Preoperative management: After birth, the following steps should be taken before the surgical operation to prepare the patient for the procedure:

- **Intravenous prostaglandin** should be started as soon as possible through a safe and secure intravenous line; otherwise, the patient will become severely acidotic due to the closure of ductus arteriosus and the resulting lower limb ischemia; more than 40 years have passed since the first clinical experiments with intravenous prostaglandin infusion for prevention of ductal closure in ductal dependent neonates; in all of these patents, including IAA, the administration of prostaglandin has allowed us to prevent emergent and out of control surgical palliation (Freedom et al. 2000).
- **Inotropic support** is at times necessary; either infusions, dopamine or epinephrine, are appropriate choices.
- **Treatment of acidosis** to reach normal acid-base status; renal function should be restored to stable condition.
- **Other organs** should also function appropriately.
- **Oxygenation** status; which includes avoidance of excessive oxygen delivery leading to an unwanted drop in pulmonary vascular resistance (PVR); then, an unnecessary decrease in PVR shifts the blood flow away from the systemic circulation toward the pulmonary vasculature; the final result would be aggravated ischemia of the distal limbs.

- **Ventilation** should be optimized: prevention of hyperventilation is necessary whether the infant has spontaneous ventilation or is intubated and mechanically ventilated; again, hyperventilation leads to an unnecessary drop in PVR followed by a shift from the systemic circulation to the pulmonary vasculature; PCO2 between 40 and 40 torr is the target of ventilation.
- The patient should be prepared in the preoperative period for the course of the operation.

Intraoperative Management

The same principles for the preoperative period should be followed in the OR; including prostaglandin infusion, prevention of hyperventilation, and avoidance of unnecessary oxygen delivery. Also, the following should be considered:

- An arterial line should be established both pre-interruption and post-interruption; for this purpose, often, the right radial artery is used for pre-interruption pressure, and the umbilical artery is used for the post-interruption pressure; the latter has two main uses, first for guaranteeing the adequacy of perfusion in lower limbs and distal organs during cardiopulmonary bypass and second, for detection of any residual gradient between ascending aorta and distal aorta after anastomosis just after weaning from bypass (i.e., inside the operating room).
- Prostaglandin infusion should be continued.
- The procedure is usually done through median sternotomy, with the deep hypothermic arrest at 18 °C; however, some surgeons and centers prefer antegrade cerebral perfusion. So, the adequacy of CNS protection should be monitored including the use of NIRS and TCD.
- At first, enough release of the ascending aorta and also, the distal aorta is done; then, ascending aorta is cannulated and the patient is cooled until deep hypothermic arrest; proximal to distal anastomosis is done at this stage.
- Then, the patient is rewarmed up to 25 °C; in this stage, VSD is repaired and finally, if there is an ASD, it is also repaired.
- Now, the patient is completely rewarmed and weaned from bypass.
- Often, inotropic support is needed for weaning from bypass.
- Care should be given to treat any bleeding, including both packed cells, cryoprecipitate, and platelets; if there is a leak through sutures of the anastomosis, the bleeding could be very severe and life-threatening.
- Intraoperative TEE is very helpful in the detection of any underlying surgical defect; especially when its data are compared with preoperative echo findings.

Postoperative management: If the procedure is done without complication, the inotropic support will be tapered up to 48 h after surgery. Pain management is an integral part of care. Then, the patient could be extubated. The following conditions could be the main reasons for unsuccessful weaning and extubation:

- **LVOT obstruction (LVOTO)**: In patients with single-stage repair, the chance for LVOTO is less than in other surgical approaches; also, in single stage repair patients, would any stricture happens, it could be relieved much more easily with balloon dilation; while in those having a conduit graft for primary surgical repair, any subsequent repair should be usually corrected using a new conduit graft; on the other hand, one of the most important predictive factors which could foresee the chance of LVOTO is the size of the aortic annulus; when it is less than 4.5 mm, the chance for future LVOTO could be increased significantly.
- **Residual surgical defects** including mainly residual VSD and residual ASD.
- **Phrenic nerve** or **left recurrent** nerve palsy: This could be a source for complications like vocal cord paralysis and/or dysphagia which are at times difficult to treat and need both patience and frequent follow-up visits; at

times, interventions like vocal fold medicalization or injection medialization laryngoplasty may be needed (Pham et al. 2014).

Usually, the above technical defects (especially the acute events) should be considered seriously, especially by the surgeons as probable technical problems hindering weaning and extubation. Further evaluation and even, reoperation may be needed.

However, a residual gradient between two sides of the anastomosis is considered negligible when it is less than 30 mmHg; however, higher gradients need more assessments by the surgeon.

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Patent Ductus Arteriosus Devices

Benjamin A. Blais, Daniel S. Levi,
and Johanna Schwarzenberger

Abstract

For the prior several decades, transcatheter device closure of large ducti in infants less than a kilogram was not frequently done and was considered the next frontier. Since the Amplatzer ADO II device (now marketed as Piccolo™ Occluder) and the Medtronic MVP™ device became available in the United States and Europe, pediatric interventionalists have started closing relatively large patent ductus arteriosus (PDA) in premature infants with weights as low as 600 g more routinely. The Piccolo device was FDA approved for this application in 2019, and though approved for use in infants greater than 700 g, it has been successfully used to close PDAs in infants 600 g and less. The MVP device from Medtronic (Minneapolis, MN) has also been used for this procedure in an off-label fashion.

Percutaneous device closure is increasingly considered becoming the standard of care for management of hemodynamically significant ducti in low-birthweight infants. The procedure itself is often short and straightforward from the interventionalist's perspective. However, while the procedure can sometimes be done at bedside in the ICU, most centers choose to do this procedure in the catheterization lab with patients that are almost universally on ventilators. The anesthesiologist's management of such small infants in the cardiac catheterization lab is therefore often the most challenging and risky part of the procedure as it requires managing ambient temperature and hemodynamics in patients who are extremely sensitive to their environment.

Keywords

Patent ductus arteriosus · Transcatheter device · Stenting · Ductal dependent blood flow

PDA Closure Small Birthweight Infants

Introduction

Procedural Indications

The indication for patent ductus arteriosus (PDA) closure can vary from neonatal intensive care unit (NICU) to NICU and even among cardiologists and neonatologists at single centers. In general, most neonates have overcirculation with left atrial and ventricular enlargement and often pulmonary edema and cardiomegaly and have failed attempts at medical closure of the ductus with

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indomethacin or acetaminophen. Many of these infants have had or are at risk for necrotizing enterocolitis (NEC) and intraventricular hemorrhage (IVH). Typically, ventricular function is well preserved, but many of these infants will be mechanically ventilated with an inability to wean from the ventilator. While many infants may be on multiple drips and even inotropic support, other infants may be much healthier and less sensitive to stressors.

Procedural Overview

The procedure for closure of PDAs in small infants is performed and guided exclusively from access to the femoral vein. Access to the femoral artery has resulted in unacceptable morbidity including risk of limb loss. Future iterations of this procedure could include access from the umbilical vessels but, even in the smallest infants, femoral vein access has proven to have a very acceptable risk profile. The femoral vein is typically accessed via a 4-French sheath, and the procedure is performed under the guidance of fluoroscopy and transthoracic echocardiography. In younger patients, umbilical lines will usually be available for both venous access and medication administration as well as monitoring of arterial pressures.

Patients are typically not heparinized although some operators may choose to give a low dose of heparin at the beginning of the procedure. The standard hemodynamic portion of the catheterization with measurements of pressures and oxygen saturations is usually not performed in order to minimize the neonate's time away from the isolette. The ductus is crossed antegrade from the right heart, typically with a soft glide catheter and wire, and is profiled by ductal angiogram and a baseline transthoracic echocardiogram. The length and width of the PDA at its largest and smallest points are measured and used to select the appropriate device, after which the glide catheter is replaced with a device delivery catheter.

Device placement is then performed under fluoroscopic guidance. Once optimal device position has been obtained, the transthoracic echocardiogram is critical in confirming the device position, evaluating for evidence of residual PDA flow, and measuring the flow gradient in both the pulmonary artery and descending aorta both before and after release. It is vital that the operator evaluate carefully for any evidence of obstruction to flow through the aorta and pulmonary arteries (Fig. 1a–d). Careful attention is also paid to the tricuspid valve function as damage to the tricuspid valve is a rare but potentially severe complication of this procedure. The use of even slight pressure with the transthoracic echo probe can cause hemodynamic instability during the procedure.

Once the device is felt to be in an adequate position, pulmonary artery patency can be further confirmed with an angiogram performed through the delivery sheath prior to release. After device release, the delivery catheter is carefully removed and a surface echo is repeated to assure that the device has remained in a safe position (Fig. 2a–d).

Risks and Potential Complications

The main procedural risks include device embolization, aortic or pulmonary artery obstruction, and injury to the tricuspid valve. In a study of 200 patients (Sathanandam et al. 2020), the risk of device embolization was 2–3%, but device retrieval was successful in all cases. Tricuspid valve damage has also been reported after percutaneous PDA closure in LBWI and can be one of the more severe complications of this procedure. The creation of severe tricuspid regurgitation can certainly contribute to hypotension and the need for additional support from the anesthesiologist.

Transthoracic echo imaging is used at time of device placement to optimize device position and reduce risk of aortic or pulmonary obstruction. However, obstruction may be underappreciated, or the device may shift after release resulting in obstruction and necessitating device retrieval and replacement or urgent surgical retrieval. If the device shifts after release, obstruction can result in the pulmonary artery (typically, left pulmonary artery [LPA]) or descending aorta. Aortic obstruction can become hemodynamically significant immediately. The Piccolo device has been shown to be easily snare retrieved, but retrieval has also resulted in tricus-

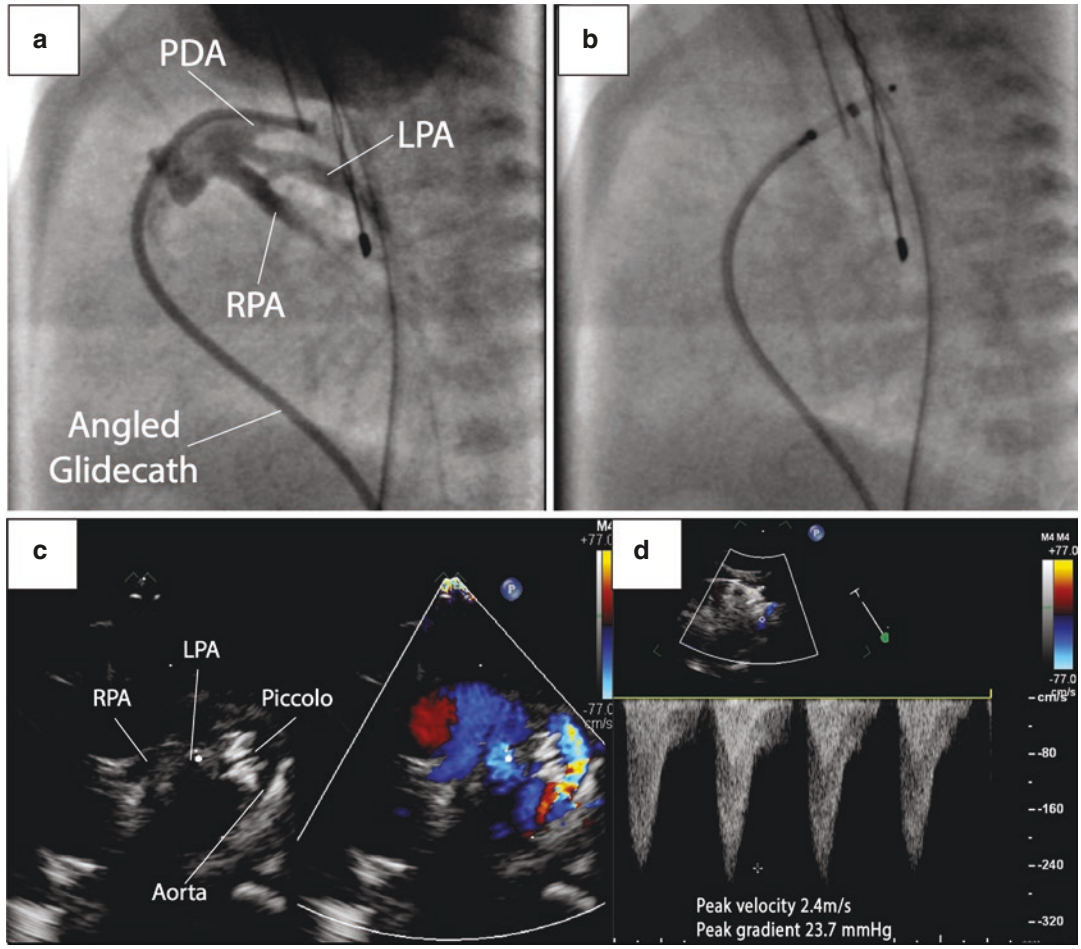

Fig. 1 Piccolo obstructed. (**a**) An angiogram in the PDA demonstrates a long PDA narrowing to 1.5 mm. (**b**) Initial deployment of a 3-2 Piccolo device. (**c** and **d**) Simultaneous echo shows the device overhangs into the aorta causing an obstruction as demonstrated by color flow aliasing and a peak gradient of ~24 mmHg under anesthesia. This device was recaptured

pid valve damage. Lastly, the Piccolo Occluder device is made with "Nitinol," a nickel–titanium alloy. Though there is no evidence for risk of a true nickel allergy, caution should be used in patients known to be allergic to nickel.

Procedural Anesthesia

Of almost all the patients brought to the congenital cardiac catheterization laboratory, these patients are by far the most fragile and need the closest attention. A regular huddle between the cardiology team, anesthesiology team, and the neonatologists is always advisable to discuss the plan prior to the procedure. Many institutions opt for a physical checklist to prepare the personnel and laboratory for these cases. The ideal environment for transport to the catheterization lab is the patient's own isolette, and thermoregulation must remain a focus if the patient is removed from this environment. Infant warming pads under the patient are advised during the procedure. Close monitoring for hypothermia is critical, and monitoring for hypoglycemia may be necessary.

Nearly all premature infants that require PDA closure are mechanically ventilated during the procedure. As access can be very challenging in patients of this size, adequate sedation to limit

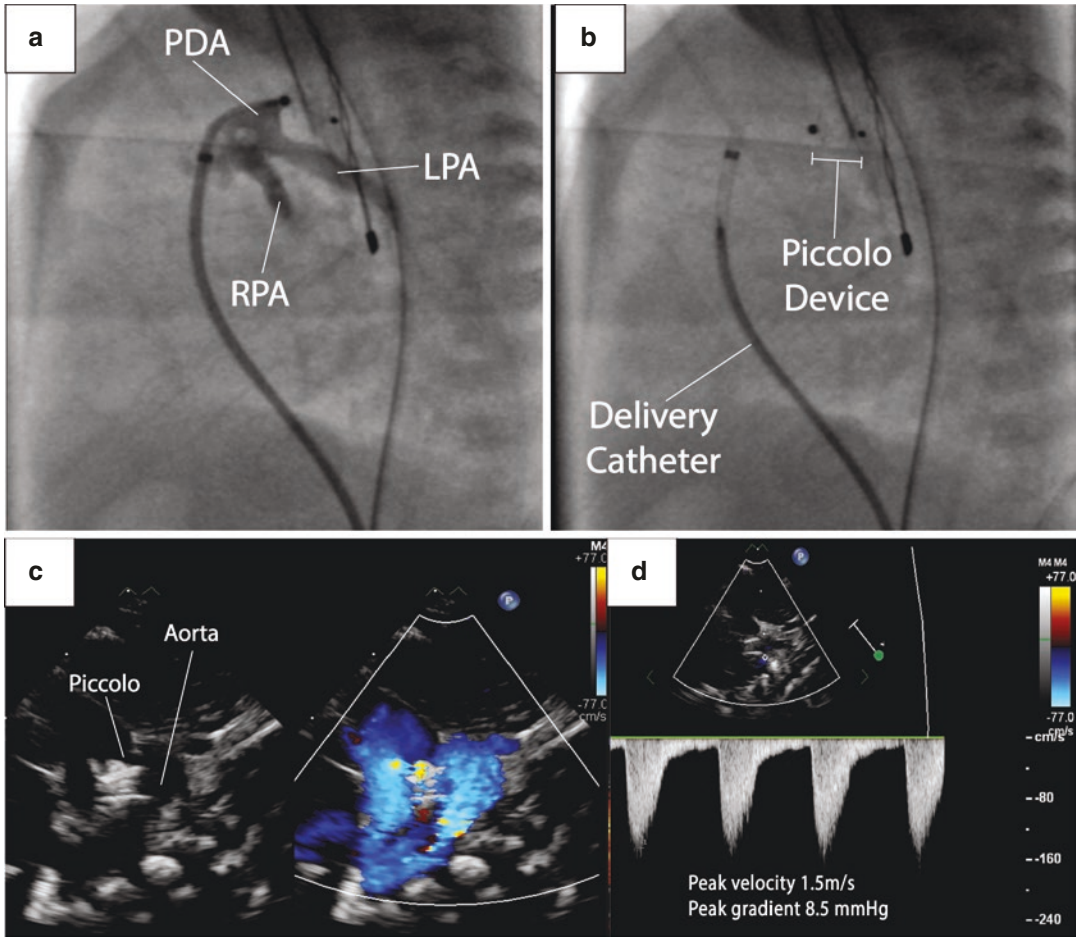

Fig. 2 Piccolo repositioned. (**a**) The 3-2 Piccolo device is redeployed and an angiogram through the delivery catheter in the pulmonary end of the PDA demonstrates no obstruction to flow to the branch PAs. (**b**) Following echo evaluation of the PAs and aorta, the device is released with favorable repositioning. (**c** and **d**) Follow-up echocardiogram demonstrates normal color flow pattern in the PAs and aorta, with normal aortic Doppler gradient

movement is critical. Although the interventionalist will not access any of the femoral or other peripheral arteries, often these patients have umbilical artery lines in place, which can be used to monitor their hemodynamics.

The extremely small size of the patient also poses unique ergonomic challenges. During the most critical part of the procedure, it is often necessary for both the interventionalist, echocardiographer, and anesthesiologist to have access to the patient. Planning, coordination, and communication are critical to allow the anesthesiologist to monitor and intervene when necessary immediately after device delivery.

PDA Device Closure Outside of the Newborn Period

Introduction

Decades prior to the advent of our ability to close PDAs in small-birthweight infants, PDA closure was one of the most commonly performed procedures by congenital interventionalists. In general, if a PDA has not closed by 1 year of age it is unlikely to close on its own. Infants and older children with PDAs have a variable severity of heart failure depending on the size of the PDA and the corresponding severity of the shunt through the

PDA. Large PDAs put children at risk for the development of left heart enlargement, heart failure, and pulmonary hypertension if not closed. Smaller PDAs may be asymptomatic and present initially with or without left-sided heart enlargement but can still impose a significant chronic volume load on the left heart over a period of many years. PDAs have been implicated in causing endocarditis, but in general very small PDAs (commonly termed the "silent ductus") less than 1.5–2 mm in width do not pose a significant risk factor for endocarditis. Many small PDAs can be followed with no need for device closure. Most pediatric cardiologists do not rush to close the "silent ductus." In general, this cohort of patients is much healthier and less prone to instability as compared to the low-birthweight infants with PDAs. Nevertheless, there are many pitfalls even to these routine procedures.

Procedural Indications

Young children with larger PDAs often have a clear indication for device closure as many of these children have gross congestive heart failure, massive cardiac enlargement, and an obvious murmur. Older children with good access to routine healthcare often present with asymptomatic smaller PDAs, though occasionally patients with large PDAs may be referred late due to lack of access to care or late detection of a murmur in the absence of symptoms. Echocardiographic findings of left heart enlargement in this population are nearly universal if the PDA is hemodynamically significant. The indication for closure in most cases is left-sided heart enlargement in the presence of a ductus that is 2 mm or more.

Procedural Overview

These children are typically at low risk for anesthesia and are hemodynamically stable but are at risk for device embolization and other complications. The goal from the interventionalist's perspective is to close the ductus with the device that is large and secure enough to minimize the risk of embolization while also being small and well positioned in the ductus enough so as not to obstruct the pulmonary arteries or aortic flow. Residual shunts, especially with coils, can be a risk for hemolysis. For this reason, cardiologists are very careful to close these defects entirely especially when using fibered coil devices. Because of the risk of hemolysis, these devices are less commonly used as of late.

In general, these procedures are done with access to both the femoral artery and femoral vein. The artery is usually used to guide the procedure with serial angiograms to confirm device position and occlusion of the PDA. The vein is used for delivery of the device with a sheath or delivery catheter. In rare cases, the procedure can be performed without arterial access using TTE guidance (as in the LBWI PDAs) and sometimes coils and the ADO II are placed from an exclusively arterial approach.

There are a range of devices available for closure of the PDA outside of the newborn period. In general the plug devices including the Amplatzer plugs in the United States and the pfm Medical © [Cologne, Germany] and Occlutech © [Helsingborg, Sweden] plug devices outside the United States are used for larger PDAs, while coils such as the NitOcclud device (pfm Medical) and Flipper coil (Cook, Bloomington, IN) are used for small PDAs. Other than the old coils, all the devices are nitinol (nickel–titanium alloy) devices without fibers. The Amplatzer™ Duct Occluder I (ADO I) and the Amplatzer™ Vascular plug are two of the more commonly used devices. These devices are easy to deploy and provide a fast and complete occlusion of most PDAs. These devices, however, are challenging to retrieve if they have embolized. The ADO I device has a recessed release screw that makes it very difficult to snare after embolization especially in the aorta. Techniques for percutaneous retrieval of this device are well described and relatively easy to perform in larger children (Sathanandam et al. 2020; Tan et al. 2005) but can be much more challenging in smaller children. The Amplatzer™ Vascular plug II device can also be very challenging to retrieve in smaller patients. The Amplatzer™ Duct Occluder II (ADO II) device is simpler to retrieve. The coil-based NitOcclud® PDA occlusion system requires more experience to deploy correctly but is less dangerous after an embolization, and it can be very simple to retrieve with a snare and 6-French sheath.

Risks and Potential Complications

Device embolization is the most significant and serious risk to these procedures (Fig. 3a–d). Ducts that are distensible and vary greatly in size throughout the cardiac cycle may be higher risk for embolization if not sized carefully. Ductal spasm may lead to undersizing of a device or the inability to safely place a device. Once a device is released, typically the operator will perform angiography immediately post-deployment to evaluate for any change in angulation or position of the device. Occasionally, repeat imaging toward the end of the procedure just prior to removing the access sheaths is repeated to re-evaluate the device position. The patient is typically observed for at least 6 h and up to 24 h after the procedure so they

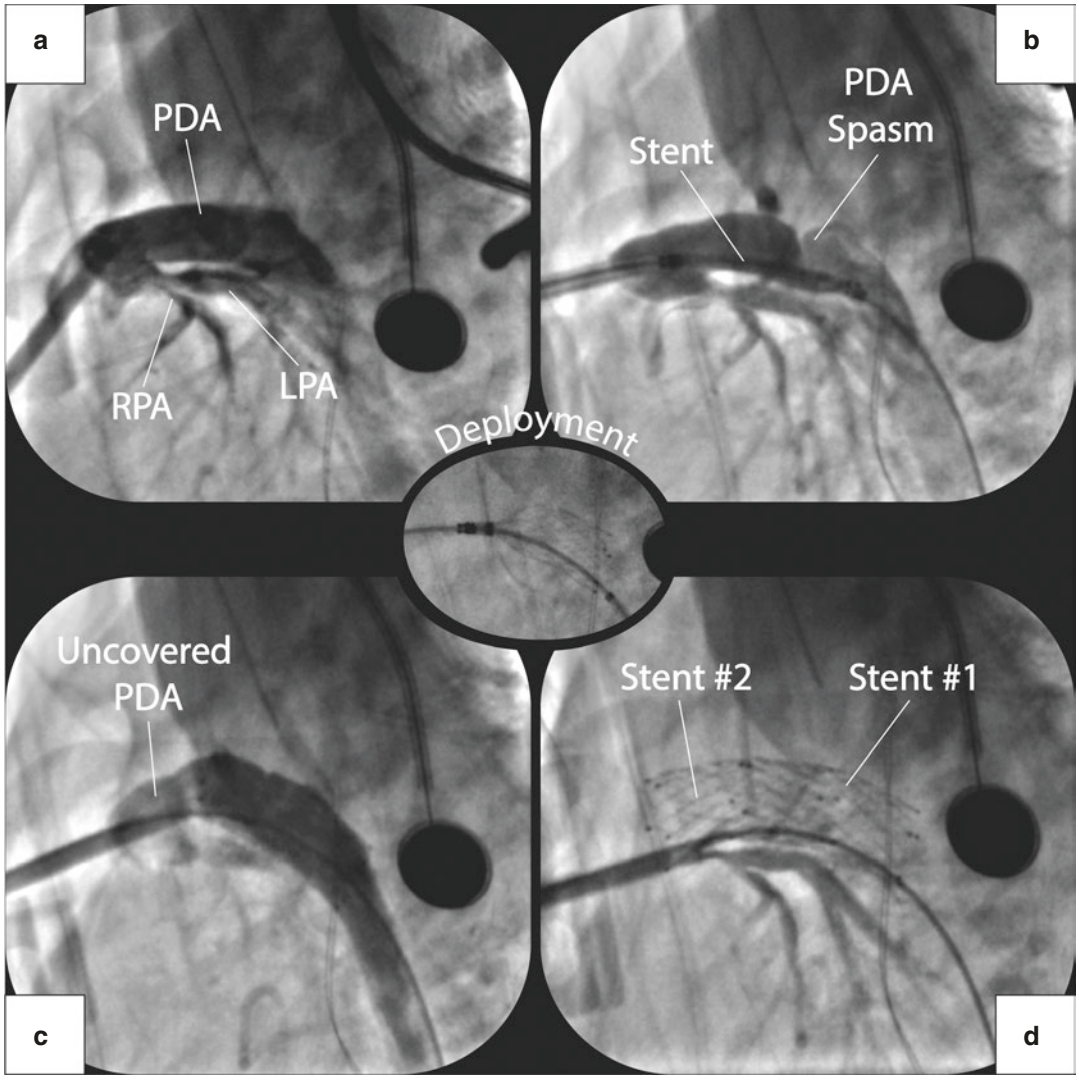

Fig. 3 PDA device embolization. (**a**) Aortic angiogram to profile the ductus shows a tubular type ductus measuring ~12 mm in length narrowing to 4.4 mm at the distal portion of the aortic ampulla. The left atrium is massively dilated as evidenced by the forced posterior curve of the NG tube as it passes behind the LA. (**b**) An 8 mm AVP II device is deployed and released with a somewhat compressed shape. (**c**) The AVP II device is seen embolized to a 2nd arcade of the left lower pulmonary artery with large delivery pin oriented proximally. Flow is obstructed to the left lower lung. (**d**) With a long 7-French Ansel sheath in the PA, the device is snared with a multipurpose goose-neck snare and retracted into the catheter

may be monitored for recurrence of murmur usually also with a chest x-ray and/or echocardiogram. Most episodes of embolization occur within hours of the procedure, but late embolization is also well described. Overall, the risk for device embolization is thought to be greatest in the first 24 h. Any device embolization to the descending aorta can be a life and limb-threatening event that has left some children paralyzed. Devices that embolize to the pulmonary artery are generally better tolerated, but a large device lodged in a proximal branch pulmonary artery is also considered an emergency. Depending on the circumstances and center experience, percutaneous device retrieval is typically attempted first, but some cases may require surgical retrieval.

In any patient at risk for pulmonary hypertension, right-to-left embolization can occur with higher PA pressures dislodging the device into the descending aorta. This is a complication that should be avoided at all costs if possible (but can occur even with an experienced operator). Most operators will use a device with retention discs on both sides such as the Amplatzer muscular VSD (mVSD) device or AVP II device in these settings. These devices allow for placement of retention discs in both the pulmonary artery and the aorta to minimize the chances of embolization (Fig. 4a–d).

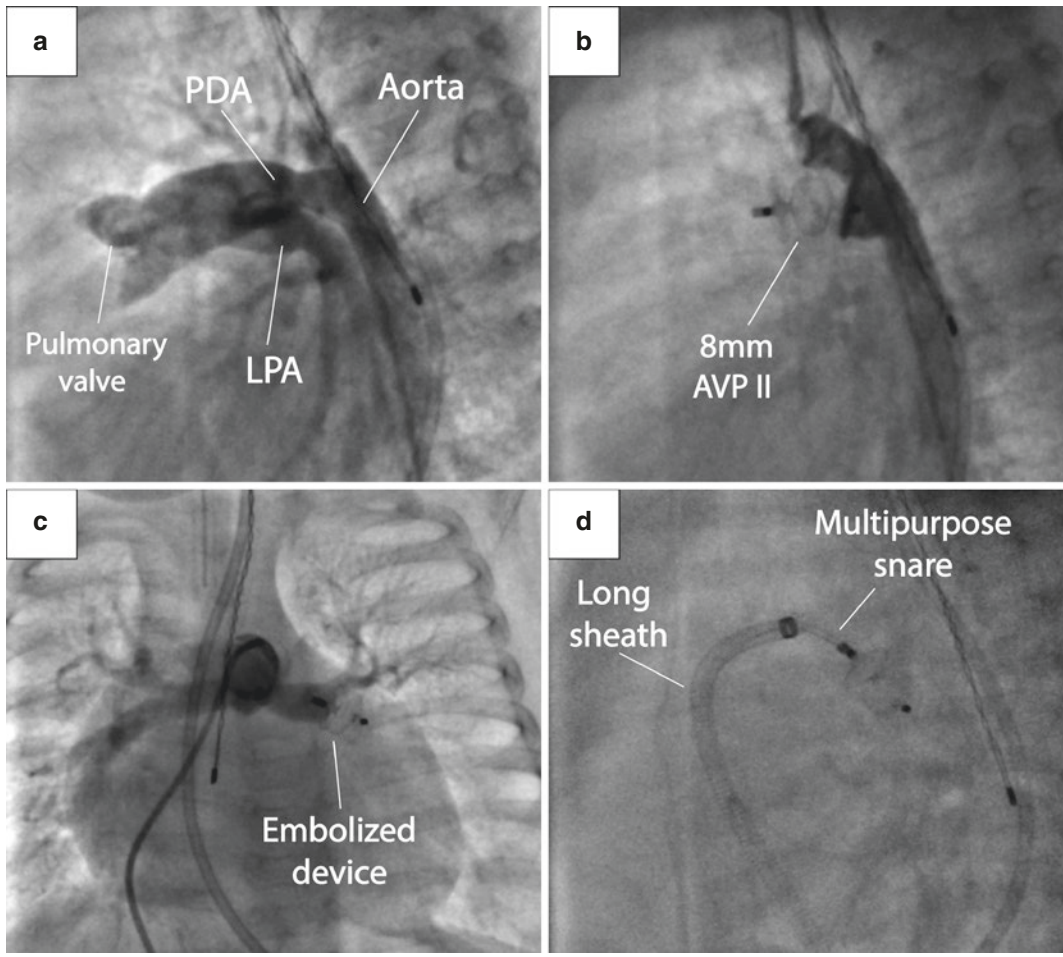

Fig. 4 PDA 2nd device. (**a**) A 10 mm AVP II device is deployed in the PDA with better device compression. An angiogram demonstrates mild compression of the proximal LPA. (**b**) Simultaneous echo shows some aliasing of color flow, with a mild gradient of 18 mmHg through the LPA. (**c**) Post-release aortic angiogram shows mild disc overhang into aorta without obstruction to flow and no residual PDA flow. (**d**) Though there is mild disc overhang into the aortic arch by 2D echo, there is no aliasing of color flow and a peak gradient of 15 mmHg

In the event of an embolization, patients are typically rushed back to the catheterization lab where they will require a second round of anesthesia and vascular access. As long as the patients remain hemodynamically stable, attempting transcatheter device retrieval is typically the first choice. However, for patients unable to tolerate the obstruction from an embolized device in the descending aorta or pulmonary artery, emergency surgery may become necessary. From an anesthesia standpoint, it is critical to monitor perfusion in the lower extremities especially if a plug-type device has embolized to the descending aorta.

The usual complications associated with large sheathes in the vein and femoral arterial access can all also come into play in these cases including both bleeding, retroperitoneal bleeding, hematomas, and pulse loss.

Procedural Anesthesia

In children less than 1–2 years of age, PDA device closure is typically done under general anesthesia. However, some institutions, especially outside the United States, will routinely perform these cases in older children under conscious sedation. Risk stratification of the patient's baseline status should be assessed and discussed among the team members prior to induction. Patients with an isolated PDA who present with moderate or large shunts may have some degree of exercise intolerance and increased work of breathing due to decreased lung compliance. Pulmonary edema is uncommon but may occur in younger patients with more advanced congestive heart failure. Cardiomegaly with left heart enlargement is common but is unlikely to increase risk of induction unless there is a concern for ventricular dysfunction.

Patients with very long-standing and hemodynamically significant PDAs are at risk for pulmonary hypertension and even Eisenmenger's syndrome due to the long-standing exposure of the pulmonary vascular bed to increased pressure and blood flow. Children with a history of premature birth and/or chronic lung disease or Down syndrome are also known to be at increased risk for elevated pulmonary pressures. In addition to the implications this has for the choice of induction and anesthetic management, these patients are also at higher risk for device embolization and, rarely, may be found to not be a device candidate based on angiography during the procedure. During the hemodynamic assessment portion of the catheter, patients with elevated pulmonary artery pressure will undergo assessment of their pulmonary vascular resistance and how they respond to vasodilating agents, typically 100% FiO_2 and inhaled nitric oxide (20–40 ppm) to help in determining advisability of ductus closure. Balloon test occlusion of the PDA may also be performed in select cases in which a right-to-left shunt through the PDA could be an essential "pop-off" for patients with advanced pulmonary vascular disease.

PDA Stenting for the Provision and Maintenance of Systemic Blood Flow

Introduction

Patients born with hypoplastic left heart syndrome (HLHS) or small left heart structures such as those seen in Shone's syndrome (classically defined as supravalvular mitral membrane, parachute mitral valve, subaortic stenosis, and coarctation of the aorta) are at risk for inadequate systemic blood flow provided by the left ventricle and may therefore be dependent on the subpulmonary ventricle to provide the bulk of the systemic circulation through the ductus arteriosus. In borderline cases of left ventricular hypoplasia, MR scans are performed preprocedurally to quantify the LV volumes in order to predict if the PDA is needed longer term. These patients may depend on prostaglandin infusions for an extended period of time to maintain ductal patency and allow for somatic growth before surgical palliation, which is typically the staged single ventricle pathway in cases of HLHS or a staged biventricular repair for more mild Shone's cases.

One available option for such patients is to proceed with neonatal stage I single ventricle palliation or other intracardiac surgical intervention

requiring cardiopulmonary bypass (CBP), circulatory arrest and, usually, nontrivial operative times. The morbidity and mortality of this procedure in the neonatal period are not trivial. If, however, the patient is deemed to be too high risk for a surgical stage 1 Norwood-type surgery, a hybrid palliation with stenting of the ductus arteriosus and banding of the pulmonary arteries may mitigate these risks by shifting the surgery to an older age and larger patient size.

PDA stenting secures a reliable source of systemic blood flow via the stabilized ductus arteriosus, and branch PA banding balances pulmonary and systemic blood flow by protecting the pulmonary bed from overcirculation and exposure to systemic blood pressure. A balloon atrial septostomy is also often performed at the time of intervention if a larger atrial-level left-to-right shunt is needed.

Procedural Overview

Patients born with HLHS or a variant of Shone's syndrome are typically hemodynamically stable in the postnatal period provided that there is an adequate atrial septal communication and that the patency of ductus arteriosus is secured with prostaglandin infusion. Typically, the hybrid procedure is performed in the first 1–2 weeks of life before significant pulmonary overcirculation has occurred. Patients are usually on no or little respiratory support and often require intubation for the procedure.

Most institutions will review the imaging and discuss the case in a multidisciplinary format that includes representation from NICU, cardiology, cardiothoracic surgery, and anesthesiology as well as other vested ancillary team members. The main consideration for the team is the general approach. Most groups choose to place pulmonary artery (PA) bands via a median sternotomy, followed by PDA stenting performed via a sheath placed directly into the main pulmonary artery (MPA). Sheath placement in the MPA may be avoided if the operator chooses to place the PDA stent percutaneously either before, during, or after the PA bands have been placed. Typically, in these cases the PA bands are performed by surgery first, as this allows for stabilization of the hemodynamics and improves surgical exposure of the LPA, which may otherwise be complicated by the PDA stent (Galantowicz and Cheatham 2005). Some groups have started to use percutaneously placed PA "bands" made from micro vascular plug (MVP, Medtronic, Minneapolis, MN) devices, allowing the entire procedure to be done without surgery (Kiene et al. 2021). Early attempts at this approach using Amplatzer™ Flow Restrictor devices led to significant hemodynamic compromise and, ultimately, poor outcome due to the need for stiff delivery cables with an obligatory course through the heart and issues with the branch pulmonary arteries. The future of the hybrid palliation will likely rely more on a completely percutaneous strategy if the experience and technology of flow-regulation devices allows for it. However, for the purposes of this chapter the most common approach of simultaneous PA banding and PDA stenting via a median sternotomy will be discussed in more detail.

Arterial access is used for intraprocedural monitoring either through a previously placed umbilical artery line or a preprocedural peripheral arterial line. Under general anesthesia a median sternotomy is made (off CBP) and bilateral branch PA bands are placed utilizing small (1–2 mm long) segments of a 3 or 3.5 mm Gortex tube graft. Once positioned, the bands are tacked to the local adventitia and tightened, first according to the patient's size and then adjusted to achieve the desired systemic blood pressure and oxygen saturation. Typically, there is a 10-point increase in systolic blood pressure and a 10-point decrease in oxygen saturation (Galantowicz et al. 2008). With the base of the main pulmonary artery (MPA) exposed, Seldinger's technique is then used to place a sheath directly into the MPA. Angiography is used to assess the tightness of the PA bands via angiograms from the sheath or from a second catheter placed in the main PA via the femoral vein (Fig. 5a, b). This picture will profile the ductus arteriosus to obtain measurements, as well as provide a road map for stent placement. The operator has a choice of balloon-expandable stents and self-expanding stents, with a more recent trend toward using more self-expanding stents. The entire ductus must be covered by the length of the

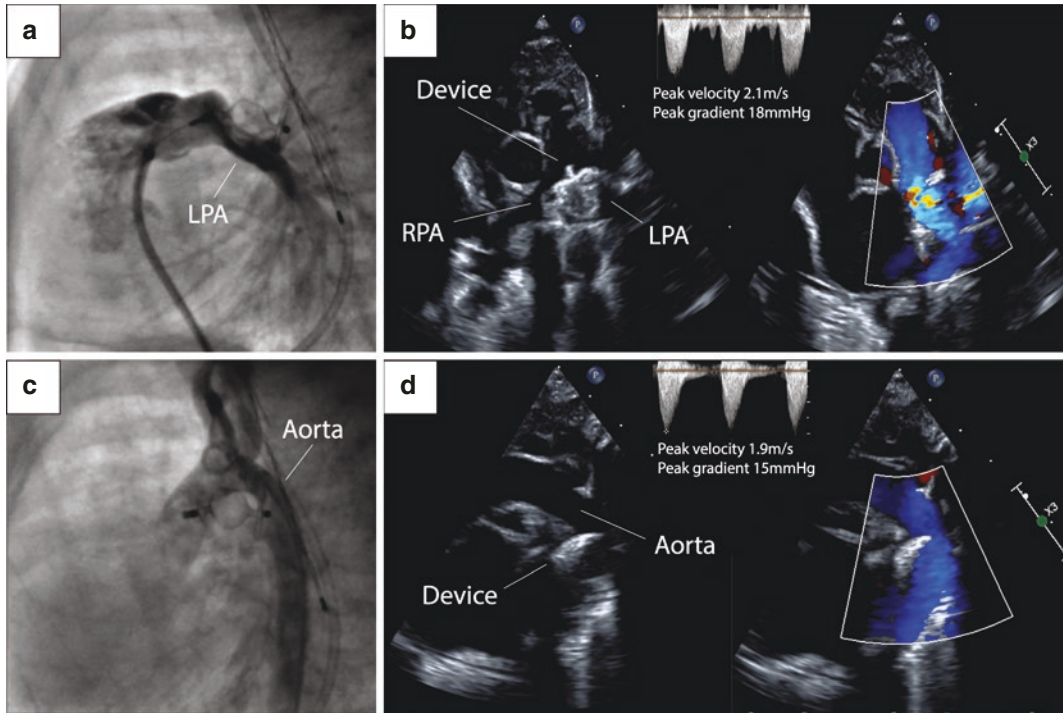

Fig. 5 Stent for systemic BF. (**a**) Initial angiogram through the access sheath on lateral shows a large PDA (8 mm × 25 mm) and tight proximal PA bands. (**b**) With wire access in the descending aorta, an angiogram is performed through the sheath to confirm positioning of a self-expanding stent prior to deployment. A kink or spasm of the PDA distally is noted. (**c**) The stent is then deployed by uncovering it. Angiogram demonstrates that the proximal portion of the PDA remains uncovered. (**d**) Angiogram through the sheath following deployment of second stent shows unobstructed flow to both PAs (image taken before PDA fills). Overlapping stents are seen in good position

stent to prevent ductal narrowing in uncovered areas (Fig. 5c, d). Because the entire ductus must be covered, often two stents are needed (especially in the long versions of these PDAs).

In cases of aortic atresia or extreme LV hypoplasia, retrograde flow in the transverse arch is needed for preservation of flow to the coronaries and head and neck circulation. In these cases, care must be taken not to jail or obstruct retrograde flow to the aorta. In especially high-risk patients, a "retrograde BTT shunt" can be placed prior to PDA stenting. In other cases, care must be taken to preserve retrograde flow back into the transverse aorta through the side of the stent for upper extremity, coronary, and cerebral perfusion. This is especially important in patients with aortic atresia and/or severely hypoplastic aortas that are at risk of ostial stenosis of the retrograde arch, kinking, or unfavorable positioning after placement of the PDA stent.

Procedural Risks

Stenting of large PDAs for the maintenance of systemic blood flow can be very straightforward but also has numerous procedural risks. All of the usual risks for open chest cardiac procedures pertain here. It is not uncommon to lose position of a sheath placed through the main PA via a purse string suture. This can result in significant acute blood loss. Rapid volume replacement and support of hypotension is often necessary. The more specific risk in this procedure is spasm or kinking of the large arterial duct. Often this can result in acute hypotension, especially in the lower extremities. An infusion of PGE is typically maintained for the case, but mechanical manipulation of the ductus can still result in spasm. As above, the most significant procedural risk is loss of retrograde flow in the arch after stenting of a large PDA. This can result in

coronary insufficiency and can result in the need for urgent extracorporeal membrane oxygenation (ECMO).

Procedural Anesthesia

Of all the PDA interventions, the hybrid approach to PDA stenting and branch PA banding is the most invasive and complex. It involves coordination between the catheterization lab and surgical teams with cardiac anesthesia. The anesthesia aspect of this procedure is more of a cardiac surgery than a cardiac catheterization. General anesthesia with a dedicated peripheral arterial line and central access is nearly uniformly established by anesthesia prior to the procedure. PGE infusion is typically continued throughout the entire procedure, and blood is uniformly made available as transfusions are sometimes needed to compensate for bleeding. Continuous monitoring of blood pressure in both the upper and lower extremities is essential to observe for either of the most common risks to this procedure.

PDA Stenting for the Provision and Maintenance of Pulmonary Blood Flow

Introduction

Stenting of the PDA for maintenance of pulmonary blood flow is becoming an increasingly common management strategy of infants born with various forms of pulmonary atresia or other lesions dependent on ductal blood flow for pulmonary circulation. Though surgically placed BTT shunts are still widely used for this indication, there are increasing data that demonstrate that PDA stenting is associated with lower mortality and less morbidity than surgical shunt. Further, PDA stent palliation has been shown to result in similar or improved growth of the PAs, decreased duration of mechanical ventilation, decreased ICU LOS, and in some cases hospital LOS, decreased diuretic burden, and lower rates of acute complications (Boucek et al. 2019). This approach may result more commonly in reintervention, but often these are planned/expected reinterventions.

If there is a second source of pulmonary blood flow (as in patients with pulmonary stenosis), the procedure is much safer, as temporary occlusion of the PDA does not result in a complete loss of blood flow to the lungs. Similarly, the morphology and takeoff of the PDA from the aorta can dictate the complexity of the procedure. Many PDAs are very straight as in the ducts typically found in patients with pulmonary atresia with intact ventricular septum (PAIVS), while others can be very tortuous and can pose additional technical challenges if they arise from the underside of the aortic arch. The origin and morphology of the PDA will determine the interventional approach: many procedures are done with femoral access, while others require carotid or axillary access. The complexity and risks of the procedure can also be dictated by whether an antegrade or retrograde approach to the PDA is required and by the propensity of the PDA to spasm. Regardless, this is always a procedure with significant risks for emergent need for support from anesthesia and for the potential need for urgent ECMO and even an emergent surgical BTT shunt.

Procedural Overview

One of the largest challenges to this procedure is the management of the prostaglandin (PGE) infusion. For PDAs that are smaller, there is sometimes not a need to stop the infusion. However, for larger PDAs, even in the presence of tortuosity, most interventionalists choose to stop the prostaglandin infusion prior to the procedure in order to allow the ductus to narrow to accommodate stenting. Since all PDAs are different, it is always a challenge to determine how long before the procedure to stop the PGE infusion. Many centers will trial the infants off of the PGE infusion in the days prior to the procedure in order to know how long it takes before the PDA starts to close and the patient begins to desaturate. This data can then be used to time the withdrawal from PGE prior to PDA stenting.

Many centers also choose to perform CT angiography prior to the procedure in order to profile the ductal shape, course, and takeoff from the aorta for procedural planning purposes. Other

centers will simply rely on surface echocardiography for procedural planning.

The approach is typically determined by the location and angle at which the PDA arises from the aortic arch. PDAs that arise from the underside of the arch are typically performed from a carotid or axillary artery approach. Both cutdowns and percutaneous approaches have been used to access these arteries (Fig. 6a–d). In cases of Tetralogy of Fallot, an antegrade approach through the heart and aortic valve can be utilized to access the PDA. For PDAs that come off arch more distally and have a favorable angle from the descending aorta, a pure retrograde approach from the femoral artery can be used for ductal stenting. In cases of PAIVS, the stenting can be done in an antegrade fashion through the pulmonary valve once it has been opened up with guidance from a retrograde catheter.

Regardless of approach, it is always necessary both to utilize the most direct approach for stent placement and to have adequate imaging to guide the procedure to allow for the stent to cover the entire length of the PDA. Imaging can be performed retrograde with a pigtail catheter from the femoral artery or with an antegrade catheter placed in the aorta. Sometimes with axillary and carotid approaches, angiograms are performed directly from the sheath used to position the stent in the PDA.

The basic procedure involves utilizing directional catheters, often in combination with a coaxial microcatheter, to position the stiffest wire possible across the ductus and into the distal pulmonary arteries. It is not uncommon to have narrowing of one or both branch pulmonary arteries at the site of ductal insertion. A preprocedural plan for management of these narrowings needs to be considered so as to avoid worsening of stenosis to either PA. Often a soft wire is utilized to cross the PDA and is then exchanged with microcatheters for a stiffer wire. The placement of stiff wires across a PDA is often the point in the procedure at which the PDA can spasm or kink, which can result in sudden desaturations and may require removal of all catheters and wires and a reconsideration of the approach.

If the wire placement across the PDA is well tolerated, a stent is then advanced through the PDA and placed just distally enough to cover the pulmonary end of the PDA (Fig. 7a–c). It is favorable if just one long stent can cover the entire PDA but often two stents are needed to line up perfectly with both the PA and aortic end of the PDA. Interventionists always try to avoid hanging significant amounts of the stent into the aorta to avoid obstruction to systemic circulation. As the stent is advanced into the ductus, especially in tortuous PDAs, the operator must also be aware the patient may suddenly desaturate and lose pulmonary blood flow from obstruction and/or ductal spasm. Stent deployment will return the pulmonary circulation as long as the spasm does not persist to a significant degree in any uncovered portion of the ductus that may persist after stent deployment (Fig. 8a–c).

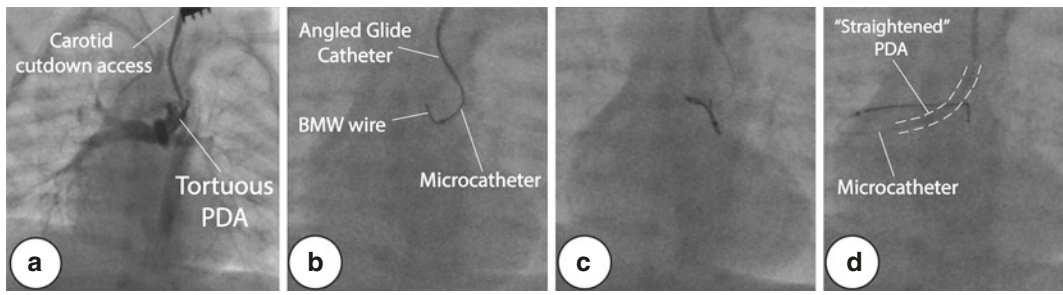

Fig. 6 Stent for pulmonary BF access. (**a**) Aortic isthmus is accessed via carotid cutdown. Angiogram through an angled glide catheter shows a serpiginous PDA. (**b** and **c**) Using the angled glide catheter to provide support, a microcatheter and coronary wire are used to cross the tortuous ductus. (**d**) With wire access established in the RPA, the microcatheter is advanced into the RPA and the ductus "straightens" out favorably

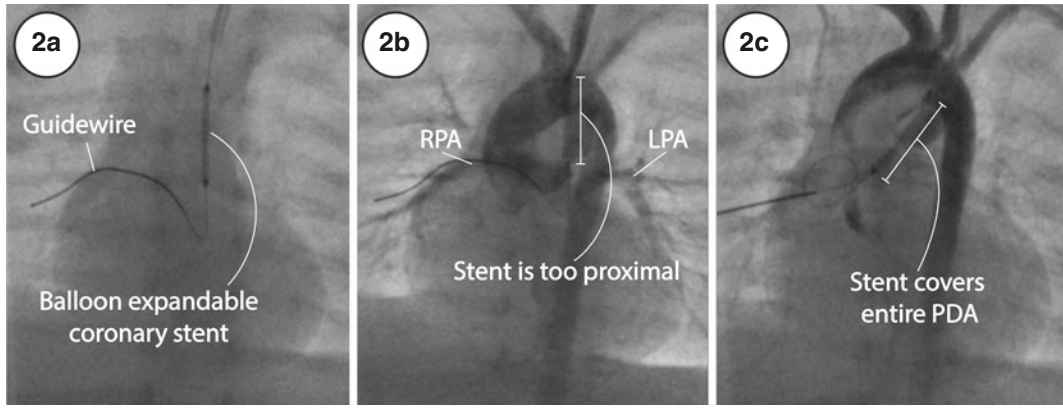

Fig. 7 Stent for pulmonary BF stenting. (**a**) A balloon expandable coronary stent with enough length to account for foreshortening on dilation is advanced across the PDA over a stiff guidewire. (**b** and **c**) Angiograms are performed through the access sheath to help position the stent to cover the entire length of the ductus without significant overhang into the aorta or jailing of a branch pulmonary artery if possible

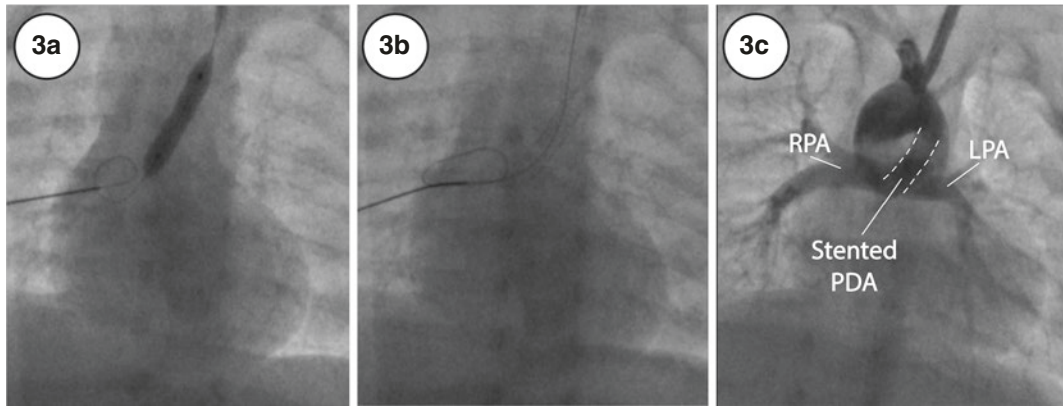

Fig. 8 Stent for pulmonary BF stenting. (**a** and **b**) The stent is deployed. (**c**) Post-deployment angiogram shows good flow through the stent with equal distribution to both lungs

Procedural Risks

PDA stenting for maintenance of pulmonary blood flow is a procedure that requires a constant assessment of PDA patency. The main risk of the procedure is spasm or kinking of the PDA resulting in prolonged cessation of pulmonary blood flow. PDA dissection is rare but has been a well-described complication of this procedure. Other procedural risks include stent embolization or migration or worsening of stenosis to a single pulmonary artery secondary to stenting (Onalan et al. 2020).

Procedural Anesthesia

More than in almost any procedure that is performed in the pediatric catheterization laboratory, this procedure involves constant communication between the pediatric cardiologist and anesthesiologist. Anesthesia should be involved with preprocedural planning including approach and timing of the cessation of the PGE infusion if this is necessary. During the procedure, the anesthesiologist should be aware of when the ductus is going to be crossed and when the PDA stenting is going to be performed. The

anesthesiologist may need to support both the blood pressure and initiate prostaglandin infusion in this case of severe spasm or kinking of the PDA. The anesthesiologist may need to make the pediatric cardiology interventionalists aware of the patient's status in the event that rapid deployment of a stent is needed, or in case it is necessary to withdraw all instrumentation from the PDA.

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Hypoplastic Left Heart Syndrome: Treatment Options

William M. Novick

Abstract

The publication by Norwood and colleagues from Boston Children's Hospital in 1983 represented a paradigm shift in the care of children with Hypoplastic Left Heart Syndrome (HLHS). The focus of this chapter will be on the first stage reconstruction and interstage period of children with HLHS, bidirectional Glenn/Hemi-Fontan, and the modified Fontan are covered elsewhere. Early operative mortality for Stage 1 reconstruction was significant but has improved significantly in several centers. The initial operation has also changed significantly over time. The knowledge gained has resulted in improved results to the point where several centers are now reporting Stage 1 mortality of less than 10%. The refinement of which technique provides the optimal outcome is undoubtedly the way forward to continued improvement in mortality.

Keywords

Hypoplastic Left Heart Syndrome
Norwood · Bidirectional Glenn
Hemi-Fontan · Modified Fontan
Sano procedure · Hybrid procedure

Introduction

The publication by Norwood and colleagues from Boston Children's Hospital in 1983 represented a paradigm shift in the care of children with Hypoplastic Left Heart Syndrome (HLHS) (Norwood et al. 1983). Before this surgical innovation children were given compassionate care only and survival without intervention was and remains zero at 1 year (Siffel et al. 2015). The focus of this chapter will be on the first stage reconstruction and interstage period of children with HLHS, bidirectional Glenn/Hemi-Fontan, and the modified Fontan are covered elsewhere. Early operative mortality for Stage 1 reconstruction was significant, 34% at 30 days, but has improved significantly in several centers (Murdison et al. 1990; Hraska et al. 2000; McGuirk et al. 2006). The initial operation has also changed significantly over time, from the central shunt originally described to modified Blalock-Taussig shunts with a tendency toward smaller shunt size. Although the Norwood oper-

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ation provided children with HLHS an opportunity for surgical intervention, several children were still dying on the first postoperative day from acute cardiovascular collapse. Jobes and colleagues at Philadelphia Children's Hospital were able to demonstrate that the precise control of CO_2 levels would ameliorate the coronary steal and provide a more optimal post-operative course (Jobes et al. 1992). Despite this discovery balance of the systemic and pulmonary circulations remained problematic sudden cardiovascular collapse was not eliminated and mortality in the late 1990s remained in the 15–20%(Bartram et al. 1997).

Concerns regarding coronary supply continued as interstage deaths following the Stage 1 Norwood procedure persisted (Barron 2013). However, in 2003, Sano and colleagues published a sentinel paper reporting on the use of a right ventricular to pulmonary artery conduit utilizing a 5 mm Gore-Tex shunt as the source of pulmonary blood flow (Sano et al. 2003).

An alternative to immediate reconstruction in the newborn was reported in 2002, this "Hybrid Procedure" included bilateral pulmonary banding and insertion of a stent in the ductus arteriosus (Akintuerk et al. 2002). Subsequently, some centers adopted the Hybrid approach as the initial palliation for HLHS.

Pathology

The pathology of HLHS is typically subdivided into 4 different subtypes. Although there are other pathological configurations for which a Stage 1 repair can be used we will only focus on HLHS. The 4 subtypes are aortic atresia with mitral atresia, aortic atresia with mitral stenosis, aortic stenosis with mitral atresia, and aortic stenosis with mitral atresia. The ascending aorta is typically quite small between 2–4 mm and this small size progresses into the transverse arch and isthmus before often ending in an area of coarctation. The spectrum of atrial septal defects ranges from intact to a widely patent secundum defect. Left ventricular size can vary from diminutive to hypoplastic. Coronary ventricular fistulae can occur although they are rare. Mild forms of HLHS merge with the pathology of Shone's Syndrome.

Diagnosis

Pre-natal diagnosis is preferred as this allows the parents the opportunity to become educated about the options for treatment and for the local team to be aware and prepared for the subsequent birth of the child (Wolter et al. 2016). A fetal echocardiogram performed by an experienced individual will delineate the defect from other congenital cardiac malformations. Any newborn with a murmur should be considered for echocardiography before discharge as some children with heart disease does not display symptoms and a few critical heart disease can exist (Al-Ammouri et al. 2015). Routine two-dimensional echocardiography with continuous and pulse Doppler analysis will fully define the intra-cardiac and aortic anatomy of the child with HLHS. Those children with highly restrictive atrial septal defects should either undergo balloon atrial septostomy or early operation as progressive deterioration can be expected if the restrictive defect is not addressed.

Pre-operative Care

The birth of a neonate with HLHS that has received a prenatal diagnosis is attended by a pediatric critical care team that institutes the infusion of prostaglandins once vascular access is secured. Elective endotracheal intubation may be performed if transport times to the tertiary care center are prolonged. Supplemental oxygen is rarely needed and if required should prompt early assessment of the intra-atrial septum. Care of the child is directed towards preparation for the operation, insuring optimal cardio-pulmonary balance, absence of infection, complete assessment of cardiac and any additional congenital or genetic disorders. The family should be thoroughly engaged during this time and discussions regarding options, prognosis, and potential complications discussed.

Stage 1 Options

Modified Norwood Procedure

The cornerstones of providing a comprehensive Stage 1 palliation for HLHS require:

1. augmentation of the ascending aorta, arch, isthmus, and resection of the coarctation,
2. creation of a systemic to pulmonary artery shunt, typically from the innominate artery,
3. atrial septectomy.

Augmentation is typically accomplished with a piece of pulmonary homograft but other materials are possible. Complete autologous tissue augmentation can be performed utilizing the distal portion of the transected main pulmonary artery.

Sano Procedure

The Sano procedure was developed to eliminate the diastolic flow into the pulmonary circulation during diastole and thus raise the diastolic and thereby mean systemic pressure to improve coronary flow and hemodynamic stability following Stage 1 correction of HLHS. The Sano procedure differs from the Modified Norwood procedure primarily by the source of pulmonary blood flow. A right ventricular pulmonary artery conduit is used rather than a modified Blalock-Taussig shunt. No systemic diastolic flow occurs with this configuration for pulmonary blood flow (Mylonas et al. 2017).

Hybrid Procedure

The hybrid procedure was originally developed for those neonates that were premature, of low birth weight, had additional non-cardiac defects, documented or presumed infection, or presented late and were critically ill. Neonates with these issues were considered poor candidates for either a routine Stage 1 reconstruction or Sano procedure. The hybrid procedure consists of the insertion of a stent within the Ductus Arteriosus, bilateral branch pulmonary artery banding, and +/− atrial septostomy. Ideally, this is performed in a hybrid operating room suite, but if not available banding in the OR followed by immediate transfer to the catheterization laboratory for stenting and possible atrial septostomy can be performed. Stenting of the ductus can be supplanted by the administration of long-term intravenous or oral prostaglandins. A significant problem that has been noted is when coarctation develops proximal to the insertion of the ductus, thus compromising coronary and cerebral blood flow.

Transplantation

Cardiac transplantation for HLHS was initiated by Bailey in 1984 when he transplanted a baboon heart into a human female newborn (Al-Ammouri et al. 2015). Since that inauspicious beginning, cardiac transplantation became a viable option for the newborn with HLHS (Bailey 2004). Survival following transplantation is excellent, but pre-transplant waiting continues to claim lives. The limiting factor is an adequate pool of neonatal or young infant donors (Bailey 2004; Carlo et al. 2016). Transplantation is now mostly reserved as a rescue procedure for heart failure after Stage 1 reconstructions or Hybrid procedures (Carlo et al. 2016).

Single Ventricle Reconstruction Trial

The Single Ventricle Reconstruction Trial was conceived and run by the Pediatric Heart Network Investigators of North America between 2005 and 2008 (Bacha and del Nido 2012). A total of 555 patients were randomized to receive either a Blalock-Taussig shunt or RV to PA conduit as their source of pulmonary blood flow in the Stage 1 reconstruction. Fifteen [15] centers participated in the study with the endpoints being either Transplantation or survival to 12 months. Patients receiving the RV to PA conduit had a survival advantage, with 74% surviving compared to 64% of those receiving BT shunts [$p < 0.01$] (Ohye

et al. 2010). However, by 14 months there was no survival difference between the RV/PA or BT shunts. Centers with high volume tended to have better outcomes with the BT shunt, most likely a reflection of a greater experience and a longer period to establish post-operative care protocols (Tabbutt et al. 2012). Another tendency that was observed but did not achieve statistical significance was for aortic atresia patients to do better with the RV/PA shunt. Perhaps this reflects the improved systemic diastolic pressure and the better coronary flow seen in the RV/PA shunt. Interstage mortality for the entire cohort was 12% and there was a significant difference between those with RV/PA conduits (6%) compared to those receiving a modified BT shunt [18%, $p < 0.001$] (Ghanayem et al. 2012). Children undergoing a Hybrid procedure were not included in the Single Ventricle Reconstruction Trial randomization.

Hybrid Procedure

The hybrid procedure was initially reported in 2002. The quote from the Giessen group's initial publication of a series of children receiving the hybrid procedure describing their rationale for abandoning neonatal reconstruction was "*The limited prognosis of patients with hypoplastic left heart (HLH) is caused by still high mortality during stage I of the Norwood procedures. Additionally, a significant number of patients die in the period between the first and second step of the staged procedure*" (Akintuerk et al. 2002). A later report by the Giessen group reported the results of 107 children who underwent the Hybrid procedure with initial mortality of 2 patients (1.2%) and an interstage mortality of 6.7% (Schranz et al. 2015). The initial Giessen group's report resulted in several institutions attempting the Hybrid approach. Galantowicz and colleagues reported the results of their Hybrid program on the first 40 patients with HLHS (Galantowicz et al. 2008) and have more recently suggested that the Hybrid procedure should be considered as one of the initial procedures performed for HLHS (Galantowicz 2013). The Giessen group suggests that based on their cumulative results since 1998 the Hybrid procedure should be a choice for the first stage of palliation for HLHS (Galantowicz 2013). Subsequent reports have shown that RV size, systolic and diastolic function are comparable in Hybrid patients to classical Norwood reconstruction patients; the incidence of ECMO rescue is less after Hybrid than Norwood procedures and that surgically placed stents have fewer adverse events compared to percutaneous placement (Holzer et al. 2010; Bacha 2013; Mitchell et al. 2016).

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Individualized Surgical Approach

Over the last two decades, a great deal has been learned about the surgical care of the child with HLHS. Twenty years ago there was only 1 option for reconstruction, the Norwood with a BT shunt, a second option for treatment was cardiac transplantation and the final option for the families was compassionate care. Today there are 3 reconstructive options for these children and although survival has improved and much knowledge has been gained, we are still faced with an average 12-month survival of 64–74%.

What do we know at this point about the surgical care of a child with HLHS (Pasquali et al. 2012)? Center and surgeon volume are important for improved survival (Bacha et al. 2008). These centers typically are those with the longest experience in the surgical treatment of children with HLHS. Patients with aortic atresia that receive an RV/PA shunt have significantly improved survival compared to those receiving BT shunts (Cua et al. 2006). Interstage mortality is significantly less for those patients receiving the RV/PA shunt (Tweddell et al. 2012). The subgroup that fares the best regardless of which shunt is used is the aortic stenosis/mitral stenosis group (Bacha and Hijazi 2005). The number of centers offering the Hybrid procedure has increased steadily over the last decade (Honjo et al. 2009; Venugopal et al. 2010). Improvement in mortality will require a more tailored approach to each child with HLHS, rather than making every child fit a particular surgical preference.

Summary

The surgical options for children with HLHS have greatly expanded over the last two decades. The knowledge gained has resulted in improved results to the point where several centers are now reporting Stage 1 mortality of less than 10%. The refinement of which technique provides the optimal outcome is undoubtedly the way forward to continued improvement in mortality.

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Double Outlet Right Ventricle

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Abstract

Anesthetizing a patient with double outlet right ventricle (DORV) requires knowledge of a wide spectrum of anatomic and physiologic variants. Caring for these patients includes everything from preparing for a patient-limited pulmonary blood flow due to either fixed or dynamic right ventricular outflow obstruction similar to tetralogy of Fallot (TOF), or preparing for one with unrestricted pulmonary overcirculation. With an incidence of 3–9/100,000 live births, this lesion is relatively rare. But the physiologic considerations of managing these patients are important to those who care for patients with congenital heart disease, both for when they encounter these patients, and also because the principles guiding the management of these patients are applicable to many others, such as those with transposition of the great arteries or TOF. Here we review the anatomic and physiologic considerations of managing these patients, and frame the chapter with clinical vignettes to highlight anesthetic management goals.

Keywords

Double outlet right ventricle · Ventricular septal defect · Mixing physiology · Pulmonary stenosis · Aortic override · Pulmonary artery override

Clinical Vignettes

Case 1

An ex-36 week, 3.1-kg, 6-week-old girl with a diagnosis of DORV and a subaortic VSD has been in the hospital for the duration of her life. The patient's respiratory status had worsened; her abdominal exam revealed a tense and distended belly; and she is now intubated. She had become increasingly difficult to ventilate, with peak pressures of 30 cmH_2O. Bloody stools prompted abdominal plain films that demonstrated portal venous gas. Her absolute neutrophil count (ANC) is 882 and she has increased bands of 20%. General surgery was consulted; and given her quick deterioration they wish to take her to the operating room for an exploratory laparotomy and possible bowel resection for her necrotizing enterocolitis (NEC).

Vital Signs: SpO_2 92%, HR 148, RR 42, BP 68/22, T 37.8 °C.

Her capillary refill is 5 s. Her urine output has been decreased at 0.5 mL/kg/h. Her transthoracic echo shows a subaortic VSD, greater than 50%

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override of the aorta and an atrial septal defect. Her remaining blood work shows a hemoglobin of 10.2 g/dL, a sodium of 130 mEq/L, a blood urea nitrogen of 24 mg/dL, a blood creatinine of 0.9 mg/dL, a pH of 7.28, a base deficit of 3, and a lactate of 3.3 mmol/L. You will be managing her care in the operating room.

Case 2

A 4.1-kg, 3-month-old male with history of DORV and subaortic VSD presents for Stamm gastrostomy tube placement for failure to thrive. His past medical history is significant for 37-week normal spontaneous vaginal delivery. He takes propranolol at home because some of his desaturation is thought to be due to infundibular muscle spasm, although parents do not endorse discrete desaturations ("Tet Spells"). He has no allergies and has had no previous surgeries.

Vital Signs: SpO_2 81%, HR 122, RR 28, BP 80/36, T 37 °C.

On exam, he is a calm and thin-appearing infant with mild perioral cyanosis. His precordium is quiet; his capillary refill is 3 s. His transthoracic echo demonstrates a subaortic VSD and subvalvar pulmonic stenosis with a peak velocity of 4.1 m/s and a dynamic component; he has normal biventricular size and function. Blood work shows a hemoglobin of 11 g/dL. His chest X-ray shows clear lung fields bilaterally. Mother states that he does well with strangers.

Background

Double outlet right ventricle is a complex lesion that accounts for many anatomic variants leading to different physiologic presentation and a varied number of surgical approaches (Fig. 1) (Anderson 2013; Anderson 2002; Aoki et al. 1994). For the anesthesiologist caring for patients with this diagnosis, many of these anatomic factors will impact the patient's clinical presentation, the physiologic principles that will guide care, and expected difficulties that may arise during their perioperative management. Here we summarize the development of DORV, as well as the anatomic, physiologic, and surgical factors that may impact care of these patients.

Double outlet ventricles (right or left) have been estimated to account for approximately 1% of congenital heart disease, and double outlet right ventricle (DORV) accounts for between 3 and 9/100,000 births (Obler et al. 2008). Vierordt, in 1898, described "partial transposition" for a lesion where only one great artery, the aorta, was transposed; but DORV was described as far back as 1703 by Mery (Obler et al. 2008; Walters et al. 2000). In 1949, Taussig and Bing described transposition of the aorta with levoposition of the pulmonary artery and a subpulmonic ventricular septal defect (Taussig and Bing 1949; Konstantinov 2009). Subsequently, Lev and Volk termed this the "Taussig–Bing Heart," part of the spectrum of DORV, when they reported a similar case in 1950 (Lev and Volk 1950). The first report of successful repair of DORV came from Kirklin and colleagues in 1957, and published as part of a series in 1964, where an intraventricular tunnel repair was used to repair DORV with a subaortic VSD (Kirklin et al. 1964).

Witham (1957) was the first to categorize "double outlet right ventricle" as a diagnosis of congenital heart disease (Witham 1957); and Neufeld and colleagues (1962) were the first to classify the lesion (Neufeld et al. 1962). But, the foundation for our current classification system came from Lev in 1972, where he grounded categorization of DORV in the relationship of the VSD to the great arteries (Walters et al. 2000; Lev et al. 1972).

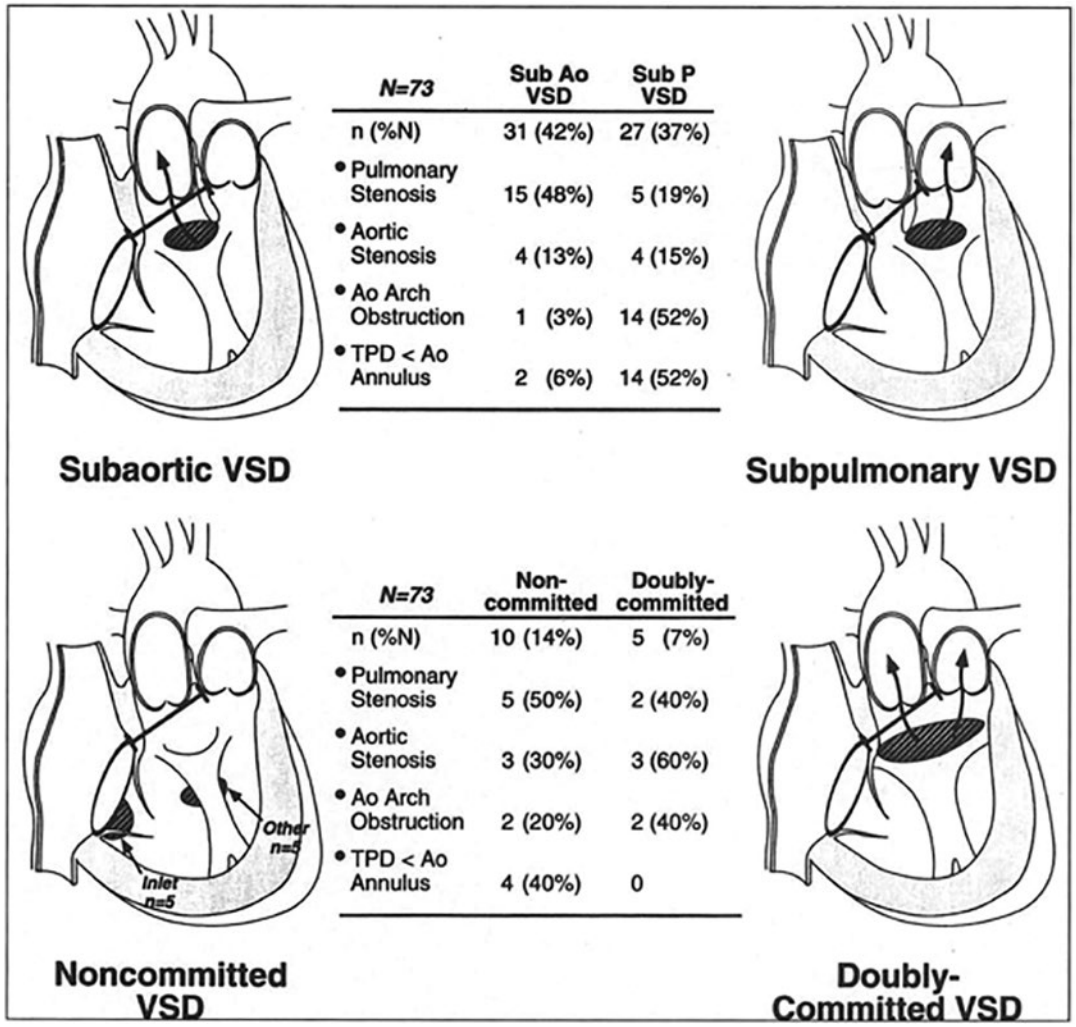

Fig. 1 Anomalies associated with double-outlet right ventricle based on VSD group. *Ao* aorta, *P* pulmonary. (Taken from Aoki et al. (1994))

Embryology

One of the earliest references to an "infundibulum" came from Keith's (Keith 1909) description of "Malformations of the Heart" to the Royal College of Surgeons in England, in part to try to explain the development of a ventricular septal defect in the context of pulmonic stenosis (Keith 1909). Our current understanding on the development of double outlet right ventricle still relies on theories of conotruncal development, particularly the segmentation and rotation, as well as growth and resorption of the conus, an embryologic structure that, in the normal heart, persists as the subpulmonic infundibulum (Jonas 2014; Restivo et al. 2006, Goor & Edwards 1973; Goor et al. 1972).

During the fifth week of embryologic development there is a partitioning of the truncus arteriosus and the conus arteriosus. The neural crest cells develop in a spiral pattern, ultimately leading to the development of outflow tracts and the great arteries. The pulmonary conus develops and becomes the infundibulum in the normal heart, separating the pulmonic valve from the atrioventricular valves with the muscular infundibulum.

Resorption of the subaortic conus leaves the aortic valve in fibrous continuity with the atrioventricular valves. The two primary theories of the development of DORV are taken from Lev (1972) and Van Praagh et al. (1970), and differ in the process by which DORV forms (Lev 1972; Van Praagh et al. 1970).

In Lev's theory, failure of the spiral septation of the conotruncus leads to a parallel arrangement of the great arteries (transposition of the great arteries) and proper septation leads to the proper arrangement of the great arteries (Jonas 2014; Van Praagh et al. 1970; Steding & Seidl 1981). Any intermediate arterial position along this spectrum (tetralogy of Fallot, DORV) occurs due to partial spiraling (Jonas 2014; Van Praagh et al. 1970; Steding & Seidl 1981).

Van Praagh proposes, alternatively, that the development of the conus and its effect on arterial arrangement determines the relative position of the great arteries. For instance, here tetralogy of Fallot (TOF) occurs due to underdevelopment of the subpulmonic infundibulum (Jonas 2014; Van Praagh et al. 1970). According to Van Praagh, development of the conus during embryogenesis brings the pulmonary artery anteriorly toward the right ventricle, and also raises it above the level of, and out of fibrous continuity with the other three cardiac valves. Underdevelopment of the subpulmonic conus would leave the pulmonic valve in a more posterior and leftward position, and the aorta more anterior and rightward. This also would cause malalignment of the conal septum with the ventricular septum, leading to obstruction from an anteriorly malaligned conal septum relative to the ventricular septum. From this theory, we can derive that DORV would involve further underdevelopment of the subpulmonic infundibulum, and possibly overdevelopment or underabsorption of the subaortic infundibulum, leading to both arteries arising from the right ventricle. Here you would see bilateral coni with both semilunar valves separated from the fibrous continuity of the atrioventricular valves. The far end of this spectrum would be transposition of the great arteries (TGA), where a subaortic conus exists without a subpulmonic conus. This leads to a pulmonic valve that lies over the left ventricle and in fibrous continuity with the atrioventricular valves while the aortic valve is outside of fibrous continuity with the other three valves and has been pushed anteriorly by growth of the subaortic conus.

No one theory completely explains the spectrum of disease, leading to controversies over criteria for diagnosis of DORV. For instance, while pathologic assessment of hearts with a diagnosis of DORV seems to support Van Praagh's theory, only 9 of 24 (37.5%) of hearts with DORV studied by Howell et al. (1991) had bilateral coni, a criterion commonly used to distinguish DORV from either TOF or TGA (Howell et al. 1991). These theories are, in any case, useful for conceptualization of the development of disease, and for the categorization of these lesions. Whether certain features are regarded as strict "criteria" or simply as "descriptors" imply the stringency with which the diagnosis is judged.

Anatomy

About 86% of patients with double outlet right ventricle have atrioventricular concordance (Walters et al. 2000); and between 72 and 77% of patients with double outlet right ventricle are able to undergo a two-ventricle repair (Bradley et al. 2007; Kleinert et al. 1997). Here we do not cover single ventricle repairs due to a poorly formed ventricle, prohibitive atrioventricular valve anatomy, prohibitive papillary muscle or chordal configuration, or other complex anatomy (Russo et al. 1988; Tchervenkov et al. 2006).

There are various classification systems for DORV. Lev (1972) initially categorized double-outlet right ventricle (DORV) based on the position of the ventricular septal defect (Lev et al. 1972). Kirklin and Barratt-Boyes (1993), as well as other authors, have asserted that this classification does not correlate to the surgical management required for repair, which makes sense when considering the multiple associated anomalies that can impact physiology, clinical presentation, and surgical repair (Fig. 1) (Kirklin et al. 1993). A more clinically relevant classification of DORV for anesthesiologist is that proposed by the Society of

Thoracic Surgeons and the European Society for Thoracic Surgery, which classifies DORV into five different subtypes (PS = pulmonic stenosis) (Spaeth 2014; Lacour-Gayet 2008):

1. VSD type: DORV with subaortic or doubly committed VSD (no PS).
2. TOF type: DORV with subaortic or doubly committed VSD and PS.
3. TGA type: DORV with subpulmonary VSD (with or without PS).
4. Remote VSD type: DORV with a remote VSD (with or without PS).
5. DORV and AVSD.

This classification allows for better conceptualization and understanding of physiologic and surgical goals.

1. VSD type: DORV with subaortic or doubly committed VSD without pulmonary stenosis (Fig. 2).

Roughly 50% of those with DORV have a subaortic VSD (Walters et al. 2000). Generally, the subaortic VSD is perimembranous, is separated by a variable distance from the aortic valve, and can extend to the annulus of the tricuspid valve, which puts it in closer proximity to the conduction system (Walters et al. 2000).

In one autopsy series, 77% of those with a subaortic VSD had bilateral coni, with the remaining 23% having a subpulmonic conus only (Walters et al. 2000). This underscores the variability of conal configuration.

Another 10% of those with DORV have a doubly committed VSD. Generally, there is either a deficient conus bilaterally with a deficient conal septum, or there can be a single conus under both great arteries (Walters et al. 2000). Some have dubbed this lesion "Double Outlet Both Ventricles," as it may be difficult

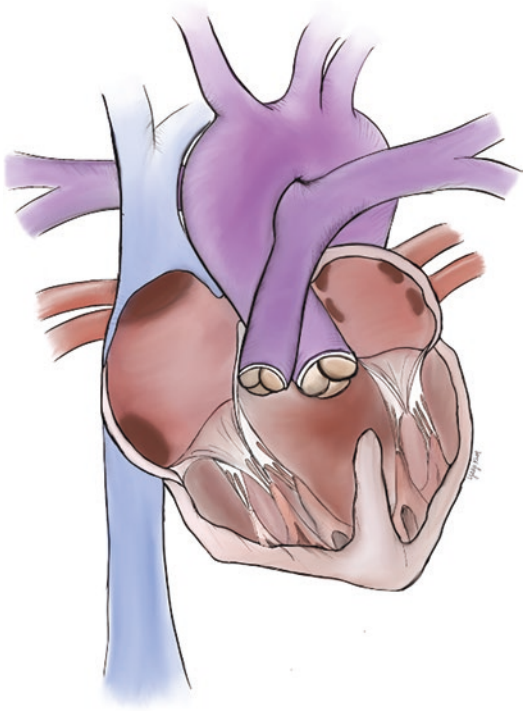

Fig. 2 DORV with subaortic VSD without pulmonary stenosis or RVOT obstruction. (Illustration by Yaeji Kim, RN, @Chd_doodles)

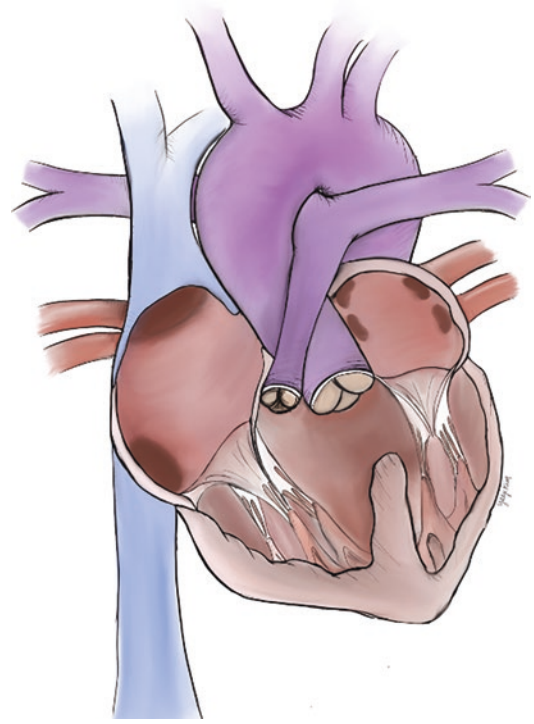

Fig. 3 DORV with subaortic VSD without pulmonary stenosis. (Illustration by Yaeji Kim, RN, @Chd_doodles)

to distinguish between DORV and DOLV (double outlet left ventricle) where a side-by-side arrangement of the great arteries overrides the VSD (Tchervenkov et al. 2000; Kirklin and Barratt-Boyes 1993).

2. TOF type: DORV with subaortic or doubly committed VSD and pulmonary stenosis (Fig. 3).

In the series by Aoki et al. (1994), 48% of those with a subaortic VSD, and 40% of those with a doubly committed VSD, had PS (Fig. 1) (Aoki et al. 1994). In their 20-year experience, Brown et al. (2001) also reported a 49% and 33% rate of PS in those with a subaortic and doubly committed VSD, respectively (Brown et al. 2001). Most of the pulmonary outflow tract obstruction that occurs in DORV is subvalvar, highlighting its similarity to tetralogy of Fallot (TOF) (Spaeth 2014).

One of the controversies in the classification of DORV is its distinction from TOF (Spaeth 2014; Jonas 2014; Mahle et al. 2008; Walters et al. 2000). Based on the theories of the embryogenesis of DORV, the amount of aortic override and fibrous continuity between the aortic valve (AV) and the atrioventricular valves (AVV) have been used. Most authors advocate the use of the 50% rule, where >50% override of the aorta into the right ventricle is required for the diagnosis of DORV (Raju et al. 2013; Bashore 2007; Walters et al. 2000; Kleinert et al. 1997). But this may be difficult to distinguish both by echocardiography and by direct inspection by the surgeon, and has little significance for management. With regard to fibrous continuity between the AV and the AVV, a significant percentage of patients with a subaortic VSD will have a subpulmonic conus only, preserving fibrous continuity between the AV and the AVV (Walters et al. 2000; Kirklin et al. 1993).

Nonetheless, DORV with a subaortic VSD and PS is part of the spectrum of DORV that poses similar management concerns to TOF for the anesthesiologist (Spaeth 2014).

3. TGA type: DORV with subpulmonary VSD with or without PS (Fig. 4).

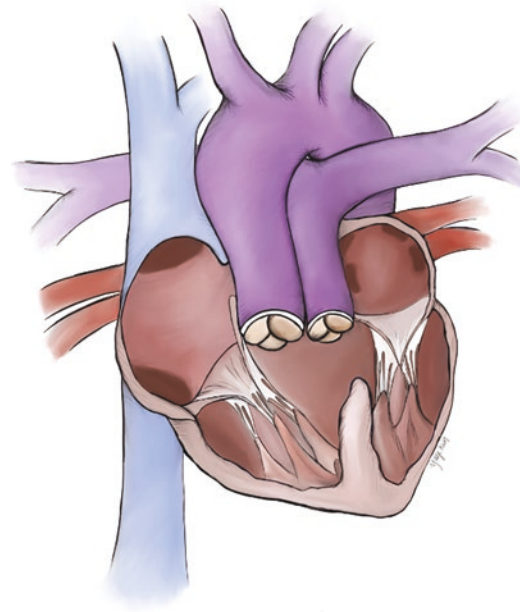

Fig. 4 DORV with subpulmonary VSD without pulmonay stenosis. (Illustration by Yaeji Kim, RN, @ Chd_doodles)

Subpulmonic VSD is present in 30–37% of DORV cases (Walters et al. 2000; Aoki et al. 1994). Generally, the VSD is unrestrictive. The Taussig–Bing anomaly, as defined by Van Praagh (1968), is a subset of DORV with a subpulmonic VSD in which there are bilateral coni with the semilunar valves at the same level (fibrous continuity between the semilunar and AVV), a side-by-side arrangement of the great arteries (L-malposed), and no PS (Van Praagh et al. 1968).

In the series by Aoki et al. (1994), of those with a subpulmonary VSD, 15% had aortic outflow tract obstruction and 52% had aortic arch obstruction of some kind, similar to the series by Soszyn et al. (2011), where incidence was 16% and 51%, respectively (Fig. 1) (Soszyn et al. 2011; Aoki et al. 1994). Arch hypoplasia is present in up to 78% of DORV with subpulmonic VSD. Pulmonary outflow tract obstruction is very uncommon in TGA-type DORV (Soszyn et al. 2011; Artrip et al. 2006; Brown et al. 2001; Walters et al. 2000; Aoki et al. 1994).

Another controversy in the classification of DORV is its distinction from TGA (Jonas 2014; Walters et al. 2000). Again, the amount of aortic override and fibrous continuity between the pulmonic valve (PV) and the atrioventricular valves (AVV) has been used (Jonas 2014). As in distinguishing between DORV and TOF, most authors advocate the use of the 50% rule, where >50% override of the pulmonary artery into the right ventricle is required for the diagnosis of DORV (Jonas 2014; Walters et al. 2000; Aoki et al. 1994). But this may be difficult to distinguish, and may not impact management. Additionally, some patients with a subpulmonic VSD will have a subaortic conus only, preserving fibrous continuity between the PV and the AVV (Walters et al. 2000; Kirklin et al. 1993).

4. Remote VSD type: DORV with a remote VSD (with or without pulmonary stenosis)

   DORV with remote (non-committed) VSD represents 10–20% of the spectrum of DORV (Walters et al. 2000). This is defined as a lesion where the distance between the VSD and the great arteries is at least the diameter of the aortic valve (Lacour-Gayet 2008; Lacour-Gayet 2002). The VSD tends to be either muscular or inlet-type, can be restrictive, and may be part of an associate AVSD (Spaeth 2014; Walters et al. 2000). Frequently, there are multiple VSDs, making surgical management difficult (Spaeth 2014; Lacour-Gayet 2008; Walters et al. 2000; Lacour-Gayet 2002). While some authors suggest that these are predominantly single ventricle lesions, some authors advocate a two ventricle repair, and at least one series by Atrip et al. (2006) reports that 70% underwent a two ventricle repair (Artrip et al. 2006; Li et al. 2014; Russo et al. 1988; Tchervenkov et al. 2006).

5. DORV and AVSD

   DORV with an atrioventricular septal defect is an uncommon lesion and usually requires single ventricle palliation, as 86% of those requiring single ventricle palliation in the series of TOF/DORV-AVSD by Raju et al. (2013) were diagnosed with DORV-AVSD (Raju et al. 2013). A total of 52% of all patients with TOF/DORV-AVSD underwent palliation rather than a two-ventricle repair. Seventy-four percent of all patients in the series had DORV-AVSD, and 26% TOF-AVSD. A significant number of patients that underwent single-ventricle palliation had Rastelli C-type AVSD (76%), hypoplastic ventricle (61%), heterotaxy syndrome (42%), as well as TAPVR (29%) (Raju et al. 2013).

Coronary Arteries

Typically with DORV, the coronary artery pattern tends to follow the rotation of the great arteries and mimics that of lesions with similar arterial position (Freire and Miller 2015). With an antero-posterior orientation of the great arteries (anterior aorta), TGA-type DORV, the coronary artery pattern is similar to that seen in TGA, with the right coronary artery arising from the posterior facing sinus, and the left coronary artery from the anterior facing sinus (Freire and Miller 2015; Walters et al. 2000; Gordillo et al. 1993). In those with a rightward and posterior aorta, the coronary artery pattern presents similarly to those with TOF (Freire and Miller 2015). There is far more variability in coronary artery pattern in those with side-by-side arrangement of the great arteries (Lowry et al. 2013; Uemura et al. 1995; Gordillo et al. 1993). Position of the coronary arteries may preclude certain surgical repairs, and should be considered before surgery (Jonas 2014).

Clinical Presentation

Clinical signs and symptoms of DORV largely depend on which anatomic variant of the disease is present.

VSD-Type and TOF-Type DORV

Half of those carrying a diagnosis of DORV will present with a subpulmonic VSD, many of those

presenting with pulmonary outflow tract obstruction (Walters et al. 2000). Most of the obstruction will be subvalvar and can present similar to that of TOF (Spaeth 2014; Walters et al. 2000). These patients may present with desaturation, whether continuous or intermittent ("TET Spells"). Management is generally focused on maintaining adequate pulmonary blood flow, maintaining adequate preload and preventing drops in systemic vascular resistance, all principles of management of TOF (Twite and Ing 2012).

In those with a subaortic or doubly committed VSD and little to no PS, the lesion relates more to an unrestricted VSD (Spaeth 2014; Lacour-Gayet 2008; Mahle et al. 2008). Children are usually mildly desaturated, but progress toward heart failure as their pulmonary vascular resistance falls over the first couple of months of life. If the patient is admitted after a late diagnosis, the patient may exhibit signs of significant overcirculation and heart failure (Spaeth 2014). These may include poor urine output, elevated blood urea nitrogen, elevated liver enzymes (alanine transferase, aspartate transferase), a lactic acidosis, as well as clinical signs of poor peripheral perfusion, such as decreased peripheral pulses or capillary refill (Simmonds et al. 2016; Panesar and Burch 2017). These patients may be receiving diuretics to decrease ventricular loading conditions or ACE Inhibitors to reduce systemic afterload (Simmonds et al. 2016; Panesar and Burch 2017). Ventilation and oxygenation may be supported with positive airway pressure in those with respiratory insufficiency or failure due to substantial pulmonary overcirculation Kato et al. 2014. Necrotizing enterocolitis has been reported in these children (Artrip et al. 2006).

TGA-Type DORV

Here, variable amounts of intracardiac mixing are possible, and will likely depend not only on the size of the VSD and the amount of override, but the presence or absence of other anomalies, such as a patent ductus arteriosus (71.9%) or an atrial septal defect (68.4%), both of which are frequently present (Spaeth 2014). These children are generally cyanotic; and interventions designed to improve intracardiac mixing of blood may be initiated (Lacour-Gayet 2008; Artrip et al. 2006). Prostaglandins are frequently initiated to maintain patency of their patent ductus arteriosus, especially in the setting of aortic arch obstruction. Balloon atrial septostomy may be required to achieve proper mixing (Jonas 2014; Spaeth 2014).

DORV with Remote VSD

DORV with a remote, or noncommitted VSD, represents between 10 and 20% of DORV (Walters et al. 2000). The clinical presentation depends on the size of the septal defect. In those with unrestrictive flow across the ventricular septum, clinical symptoms will progress in the same fashion as those patients with a VSD-type or doubly committed VSD without PS. They may have significant pulmonary overcirculation, and if they present late, may manifest symptoms of heart failure.

DORV with AVSD

Presentation of patients depends on the balance between systemic and pulmonary blood flow. Brown et al. (2001) report that 25% of these patients present with pulmonary outflow tract obstruction, which would limit pulmonary circulation (Brown et al. 2001). These patients would likely require maneuvers to improve pulmonary blood flow, which include supplemental oxygen, adequate ventilation, appropriate acid-base status, and possibly the use of prostaglandins to maintain patency of a patent ductus arteriosus (Spaeth 2014). The presence of other lesions, such as heterotaxy syndrome or total anomalous pulmonary venous return, will change the clinical picture (Spaeth 2014; Lacour-Gayet 2008). Please refer to chapters that address these specific lesions for clinical presentation.

Surgical Repair

Timing of surgery is usually early in life, with most advocating repair within the neonatal period, regardless of where in the spectrum of DORV the lesion lies (Jonas 2014; Soszyn et al. 2011; Lacour-Gayet 2008). For most cases of DORV a biventricular repair is possible (Lacour-Gayet 2008; Brown et al. 2001). As stated previously, DORV with a remote VSD, or that associated with an AVSD, are more likely to undergo single ventricle palliation (Artrip et al. 2006; Aoki et al. 1994; Russo et al. 1988).

VSD-Type and TOF-Type DORV

Generally, DORV with a subaortic VSD, with or without PS, and those approaching the mid spectrum of DORV, can successfully undergo an intraventricular baffle repair (Spaeth 2014; Jonas 2014; Walters et al. 2000). With an anatomy similar to TOF, a patch closure is possible whether the diagnosis is DORV or TOF. As the distance between the aortic valve and the VSD widens, in the presence of a subaortic conus, a baffle is needed to direct blood from the left ventricle to the aorta (Spaeth 2014; Jonas 2014; Mahle et al. 2008). In many of these cases, the VSD will need to be widened to achieve a caliber adequate for tunnel repair (Mahle et al. 2008). As the aortic valve moves further superiorly and away from the VSD, the pulmonic valve is brought closer to the tricuspid valve. When this distance becomes narrower than the diameter of the aortic valve, the baffle is at risk for late development of restrictive flow (stenosis) of the tunnel (Jonas 2014).

Mid-Spectrum DORV or TGA-Type DORV with PS

As the distance between the pulmonary artery and the tricuspid valve becomes prohibitively close for an intraventricular repair, a Rastelli repair is typically used to create a biventricular repair (Jonas 2014; Brown et al. 2001). Here the main pulmonary artery (MPA) is divided and the proximal MPA stump is oversewn. An intraventricular baffle is created from the VSD that directs blood to the aortic valve; and subsequently a homograft conduit is used to direct blood from a right ventriculotomy to the distal divided segment of the MPA (Jonas 2014; Mahle et al. 2008; Brown et al. 2001).

An alternative, less common, repair is the REV repair, a pulmonary translocation to a right ventriculotomy with a Lecompte maneuver that requires division and reanastomosis of the ascending aorta (Jonas 2014; Borromée et al. 1988). Because there is a higher incidence of pulmonary regurgitation with this repair, it is usually reserved for patients with low preoperative pulmonary pressures (Jonas 2014). Given that the pulmonary artery is usually under tension, care must be taken to avoid direct compression of an anterior coronary artery.

Lastly, aortic root translocation, or the Nikaidoh Procedure, can be used for TGA-type DORV with PS (Jonas 2014; Nikaidoh 1984). The aortic root translocation is accomplished by dividing the aorta with its valve and moving it posteriorly. This may involve coronary reimplantation. The pulmonary artery is also divided, the proximal stump oversewn, and a homograft used to connect the right ventricle to the MPA.

TGA-Type DORV

The arterial switch operation is the standard approach for DORV with a subpulmonic VSD and no PS (Taussig–Bing heart) (Jonas 2014; Mahle et al. 2008; Brown et al. 2001; Masuda et al. 1999; Konstantinov 2009; Tchervenkov & Korkola 2001). The operation proceeds in the same fashion as that for TGA.

Aortic Outflow Tract Obstruction and Aortic Arch Hypoplasia

Alternatively, Damus–Kaye–Stanzel procedure with a right ventricle to pulmonary artery conduit may be used in cases of aortic outflow tract obstruction, including those with associated aor-

tic arch narrowing or interruption (Spaeth 2014; Brown et al. 2001; DeLeon et al. 1991).

Outcomes

In their 20-year experience of repair of DORV, Brown et al. (2001) report an early mortality of 4.8%, with AVSD and aortic arch obstruction as risk factors for higher early mortality (Brown et al. 2001). In this series, 63% of high-risk patients underwent single ventricle palliation with 90% survival at 15 years, and patients from three different risk groups had a 95.8% (low risk), 89.7% (intermediate risk), and 89.5% (high risk) survival at 15 years. Their freedom from reoperation at 15 years was 87%, 72%, and 100% for these same risk categories. Artrip et al. (2006) reported surgical mortality rates of 0% for VSD-type DORV repairs, 6% for TOF-type repairs, 9% for noncommitted VSD-type repairs, and 11% for TGA-type repairs (Artrip et al. 2006). This highlights the variable anatomy of, and variable surgical options for, DORV and the increased mortality associated with more complex repairs (Bradley et al. 2007). In one of the largest series of 393 patients published, for patients complex DORV, Rastelli-type repair was associated with increased early reintervention and greater late mortality, whereas arterial switch operation was associated with greater early mortality, but improved long-term survival (Bradley et al. 2007).

Anesthetic Management of Clinical Cases

Case 1

This patient's DORV is that of VSD-type with unrestricted flow toward her lungs. This patient is 6 weeks old, and likely presented with worsening heart failure and overcirculation as her pulmonary vascular resistance fell. And while NEC is less likely in full-term infants, it has been reported in at least one patient with DORV and an unrestricted VSD-type DORV (Artrip et al. 2006). Her respiratory failure is likely a combination of her NEC and her significant pulmonary overcirculation (Spaeth 2014; Hillier et al. 2004; Panesar and Burch 2017). The patient is critically ill. With regard to management of non-cardiac issues, she will require significant fluid resuscitation, as maintenance and third space losses can equal more than 10–15 mL/kg/h (Hillier et al. 2004; Spaeth et al. 1998). Her hemoglobin is low, and she is predisposed for diffuse intravascular coagulation. She is also hypotensive. With regard to her VSD-type DORV, her pulmonary overcirculation is preventing adequate oxygen delivery to her end organs, including her gut and her kidneys. Goals will include mitigating this left-to-right shunt while improving systemic oxygen delivery.

Given that she is already marginally hypotensive, she will require hemodynamic support, particularly because she will receive anesthetic medications that will likely worsen her hypotension. Induction may proceed with careful dosing of intravenous induction agents aimed at preventing further hypotension through large drops in systemic vascular resistance or decreasing function. This may include combinations of ketamine, midazolam, or titrated doses of opiate (fentanyl) along with muscle relaxant. Ventilation and oxygenation should maintain her baseline oxygen saturations with the understanding that full saturation and hyperventilation will increase the left-to-right shunt, which should be avoided (Spaeth 2014). This patient will need a central venous catheter and an arterial line for hemodynamic monitoring and inotropic support, as well as one or two peripheral venous catheters for resuscitation with blood products and intravenous fluid. An inotrope, such as dopamine or epinephrine, may be started to augment her systemic oxygen delivery. She will need ongoing transfusion of packed red blood cells along with plasma, and possibly platelets.

Case 2

This represents a TOF-type DORV, per the STS and ESTS classification. In most of these, the

obstruction is subvalvar and may have a dynamic component (Spaeth 2014; Walters et al. 2000). This patient is in stable condition, but desaturated. This desaturation is likely attributable his dynamic obstruction, but also possibly to intraventricular mixing. These children will likely not suffer from poor peripheral perfusion, because blood flow to the systemic circulation is not limited. And although parents report no intermittent desaturations, it is not uncommon for patients to experience these "Tet Spells" once exposed to the stress of manipulation, induction, intubation, and surgical stimulus.

Although his mother reports that he does well with strangers, the stress of induction may cause stress, even if parental separation does not. A preoperative intravenous catheter is not always present for these children, particularly if they are coming to the hospital from home. Mask induction with 100% oxygen is appropriate in those without venous access, as diminished pulmonary blood flow is a concern (Twite and Ing 2012). In case of infundibular spasm, volume, such as albumin or crystalloid fluid boluses, blood cells (useful here given his low hemoglobin level), phenylephrine or femoral artery compression to increase afterload are first line therapies to ameliorate infundibular spasm (Twite and Ing 2012). Beta-blockers, such as esmolol, may be useful, but not commonly necessary, as an infusion to mitigate the inotropic and chronotropic effects of sympathetic outflow on the myocardium, and consequently infundibulum (Twite and Ing 2012). Avoiding light anesthesia and maintaining adequate preload are integral to preventing infundibular muscle spasm in TOF-like physiology (Twite and Ing 2012). Multiple anesthetic agents are acceptable for induction and maintenance of anesthesia. Ketamine, fentanyl, and/or midazolam are common agents given to supplement a mask induction and maintenance of anesthesia with volatile agent. Ketamine has been shown to increase afterload and improve oxygen saturation in those with infundibular spasm, but may decrease pulmonary blood flow in those with the most severe pulmonary outflow tract obstruction (Jha et al. 2016).

Anesthetics should be geared toward tracheal extubation in those children in whom extubation is not contraindicated. For this reason, regional anesthetic techniques may be useful in providing the patient comfort and preventing response to stimulation, while minimizing use of opiates intraoperatively. These include, but are not limited to erector spinae plane blocks, transverse abdominus plane blocks, and caudal epidural anesthesia.

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Double Outlet Left Ventricle

Zoel Augusto Quiñónez and Jamie W. Sinton

Abstract

Most of us will encounter few, if any, patients with double outlet left ventricle (DOLV), but the significant anatomic variation requires an understanding of a broad spectrum of pathophysiology. This ranges from a lesion similar to that of a tetralogy of Fallot (TOF)-type DORV, with a pulmonary outflow obstruction that may be dynamic in nature, to that of left-sided obstructive lesions and pulmonary overcirculation. Here we review the anatomic and physiologic considerations of managing these patients and frame the chapter with clinical vignettes to highlight anesthetic management goals.

Keywords

Double outlet left ventricle · Ventricular septal defect · Mixing physiology

Background

Double outlet ventricles (right or left) have been estimated to account for approximately 1% of congenital heart disease. Of the double outlet ventricles, 5% of those are double outlet left ventricles (Van Praagh et al. 1989). Double outlet left ventricle (DOLV) has a reported incidence of 1 in 200,000 (Fukuda et al. 2004) with a male predominance (Imai-Compton et al. 2010). This abnormality was first reported as early as 1819 (Coto et al. 1979). Given its rarity, the vast majority of literature describing DOLV is limited to case reports and case series (Anderson 1974; Brandt et al. 1976; Bharati et al. 1978; Paul et al. 1970 and Sharratt et al. 1976).

Nomenclature

Double outlet left ventricle, as the name suggests, describes origin of both great arteries from the morphologic left ventricle (Manner et al. 1997; Tchervenkov et al. 2000). More specifically, the whole of one great artery and at least half of the other must originate from the left ventricle (Stegmann et al. 1979).

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Embryology

Double outlet left ventricle was considered to be an embryologic impossibility until the 1960s (Sakakibara et al. 1967). One decade later, the embryologic origin of DOLV was attributed to three distinct embryologic processes: leftward shift of conoventricular junction, conotruncal (bulbar) inversion, and absorption of the conus (Coto et al. 1979; Otero Coro et al. 1981; Manner et al. 1997). At this time, complete absence of conus was a diagnostic criterion.

More recently, the leftward shift of the conotruncus, as well as errors in differential conal growth and conal absorption have been implicated as etiological components of DOLV (Otero Coro et al. 1981; Sakakibara et al. 1967; Anderson et al. 1974; Tchervenkov et al. 2000). These abnormalities result in a relative malalignment of the ventricular septum, which explains DOLV in a chick fetus. In this case report, the ventricular septum was aligned in the frontal plane (instead of obliquely) and anterior to both great arteries. The portion of the ventricular septum involved in the malformation was the subarterial portion above the crista supraventricularis and this is the most common location for an associated ventricular septal defect (VSD) (Manner et al. 1997). Abnormalities of conotruncal or bulbar inversion create improper great arterial interrelations. Finally, overzealous absorption of the conus leads to conal deficiencies.

Anatomy

As with any cardiac defect, DOLV represents a spectrum of disease. Common anatomic anomalies include a ventricular septal defect and pulmonic stenosis (Brandt et al. 1976; Coto et al. 1979; Stegmann et al. 1979; Menon and Hagler 2008). See Fig. 1 panel A for a schematic drawing of an oblique section through the heart and panel B for an echocardiographic equivalent taken from an apical view (reprinted with permission).

Figure 1 shows an anatomical depiction of DOLV. Panel A emphasizes several features of this lesion: the subarterial location of the VSD

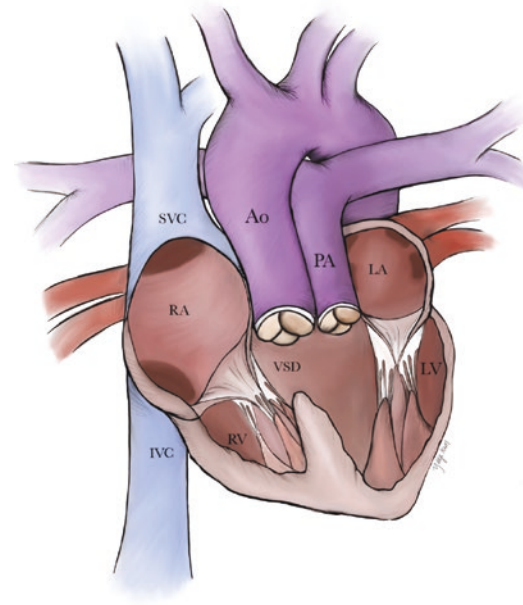

Fig. 1 Double outlet left ventricle with the ventricular septal defect positioned in the most commonly reported subaortic position

and greater than 80% override of the aorta. Also notable is the thickened, underdeveloped right ventricle and enlarged right atrium. Egress from the right ventricle is across the VSD leading to right ventricle (RV) hypertrophy and right atrial (RA) enlargement. Oxygenation status of blood is represented in color. The great arteries are equally saturated and represented in purple. Although not pictured here, pulmonic stenosis can be associated with DOLV. Panel B shows an apical four-chamber transthoracic echocardiogram view of a human with DOLV. Great arteries in this image appear to be side by side and the VSD is likely restrictive. By two-dimensional echo, it is unclear if pulmonic stenosis is present.

Situs

Segmental situs is overwhelmingly situs solitus (Brandt et al. 1976; Bharati et al. 1978; Coto et al. 1979). In a small case series, four of the five subjects had situs solitus (Brandt et al. 1976). Atrioventricular connections vary and

can include a single atrioventricular valve, a mitral valve with a deficient anterior commissure, or two atrioventricular valves (Coto et al. 1979). Mitral and pulmonary fibrous continuity may exist due to the relatively posterior position of the pulmonary artery (Brandt et al. 1976). The so-called truncal septum describes the aortic and pulmonary fibrous ridge (Brandt et al. 1976). Aortic-mitral fibrous continuity is also observed. In the available reported cases, most had D-looped ventricles (Brandt et al. 1976). By Van Praagh notation, many individuals with this lesion would have S, D, D.

VSD

Ventricular septal defects are usually subarterial or type I (Brandt et al. 1976; Minette and Sahn 2006). Pulmonary stenosis is usually related to subpulmonic muscular obstruction, although supravalvar obstruction has been reported (Brandt et al. 1976). See conus considerations below. In patients with a subaortic VSD, pulmonary outflow obstruction is universal (Alehan and Hallioglu 2003). In approximately 10% of DOLV, the VSD is doubly committed; it is associated with complete absence of subarterial conus resulting in fibrous continuity of aortic, mitral, and pulmonary structures (Menon and Hagler 2008).

Great Vessels

Positional variations in the great vessels are expected. Aberrant conal growth or absorption leads to insufficient separation of the semilunar valves (Stegmann et al. 1979). Anterior and rightward aorta (D-malposition) occurs in half of the cases (Menon and Hagler 2008; Sohn et al. 2008). Side-by-side great artery interrelation occurs less frequently and is associated with transposition-like physiology (Brandt et al. 1976; Menon and Hagler 2008). L-malposed great vessels with a doubly committed VSD and pulmonic stenosis have been described as well (Lilje et al. 2007).

Conus

Subaortic and subpulmonary coni lie between the ventricles and truncus. Conal anatomy in DOLV is variable. Complete absence of the conus had been a necessary criterion for diagnosis (Brandt et al. 1976); however, all types of conal configuration have now been described. Deficiency of subaortic conal muscle with a short, stenotic subpulmonary conus is common. Differential conal growth hypothesis explains this phenomenon. Hypoplasia of the subaortic conus leads to a posterior and inferior position of the aortic valve. In a similar way, insufficient development of the subpulmonary conus results in a posterior and inferior position of the pulmonic valve (Stegmann et al. 1979).

Coronaries

Coronary anatomy varies but the noncoronary sinus lies anteriorly and the left anterior descending and left circumflex arteries pass in front of the pulmonary artery (Brandt et al. 1976). Single coronary anatomy is also possible (Brandt et al. 1976). One left and two right coronaries have been described (Luciani et al. 2014).

Conduction System

The conduction system may be normal in DOLV. The atrioventricular node and bundle of His are normally positioned (assuming atrioventricular concordance) (Tchervenkov et al. 2000). The Bundle of His may lie along the left side of the inferior margin of the subarterial VSD, in which case, if it is closed as in a perimembranous VSD, heart block can be avoided (Bharati et al. 1978).

Tricuspid Valve

Tricuspid stenosis, tricuspid atresia, displaced tricuspid orifice, and Ebstein's anomaly have all been documented as part of DOLV. This Tricuspid

Valve incompetence can hinder antegrade flow during each cardiac contraction, especially when the VSD is restrictive, and lead to inadequate cardiac output.

Associated Anomalies

Many coexisting cardiovascular defects have been described. Atrial septal defects and ventricular septal defects are the most common associations (Imai-Compton et al. 2010). Atrial septal defects may be due to fenestration of the septum primum (Brandt et al. 1976). Either ventricle may be hypoplastic (Brandt et al. 1976). Ebstein's anomaly has been described in two cases (Brandt et al. 1976; Bharati et al. 1978). In another case, unbalanced complete atrioventricular canal, hypoplastic left ventricle, and totally anomalous pulmonary venous return coexisted (Ozkutlu et al. 2008). Reported non-cardiac anomalies include oral clefts, trisomy 21, cryptorchidism, and hypertelorism (Imai-Compton et al. 2010).

Physiology

Systemic venous return flows from the morphologic right ventricle across the ventricular septal defect as the right ventricle does not connect with either outflow tract. As the right ventricular blood is deoxygenated when it enters the left ventricle, systemic cyanosis can be expected and reported (Stegmann et al. 1979). The two most common anatomic variants not surprisingly represent the two most common physiologies associated with DOLV: first, a subaortic VSD with pulmonary stenosis may present similar to tetralogy of Fallot, second, a subaortic VSD and left anterior aorta may present with transposition physiology (Menon and Hagler 2008).

Physical Exam

Patients are invariably cyanotic (Brandt et al. 1976). Tricuspid stenosis, tricuspid atresia, displaced tricuspid orifice, and Ebstein's anomaly have all been documented as part of DOLV. This Tricuspid Valve incompetence can hinder antegrade flow during each cardiac contraction, especially when the VSD is restrictive, and lead to inadequate cardiac output (Lopes et al. 2001; Alehan and Hallioglu 2003).

Electrocardiogram

The electrocardiogram (ECG) often reveals ventricular hypertrophy (Brandt et al. 1976). The electrical axis of the heart may be negative or positive (Brandt et al. 1976). Complete heart block has been associated with DOLV even prior to surgical intervention (Brandt et al. 1976).

Chest Roentgenogram

Pulmonary vascularity is often normal to oligemic if there is associated pulmonary stenosis and rarely plethoric (Brandt et al. 1976). In one case series, cardiothoracic ratio ranged from 45 to 68 (Brandt et al. 1976) and was usually within normal limits.

Diagnosis

Multiple authors define double outlet left ventricle as requing that more than 50% of each of the great arteries arise from the left ventricle (Brandt et al. 1976). Some advocate a more conservative override of at least 80% to prevent the overdiagnosis of this rare lesion maximal great vessel overrides into the right ventricle of at least 80% has also been proposed (Menon and Hagler 2008).

Clinical presentation invariably involves cyanosis. This sign attracts medical attention (Lopes et al. 2001; Alehan and Hallioglu 2003). Later findings include non-specific signs such as heart murmur and failure to thrive.

Initially cardiac catheterization and angiography were used to define the relation among the ventricular septum and great arteries (Anderson et al. 1974). Adjunctive ventriculography has been advocated as well (Coto et al. 1979; Brandt

et al. 1976). In particular, the left anterior oblique fluoroscopic projection profiles the ventricular septum and can define great vessel origins in relation to it. Superimposed oblique views (right and left anterior oblique) can assess great arterial origins and positions in relation to each other (Brandt et al. 1976). Due to the myriad of co-existing anatomical considerations, cath imaging for the purpose of anatomic and physiology characteristics and surgical planning is practical.

Echocardiogram is a less invasive, modern diagnostic test for DOLV (Lopes et al. 2001; Alehan and Hallioglu 2003). Transthoracic images in the parasternal long axis and subcostal views demonstrate the origin of the great arteries and aid in diagnosis (Menon and Hagler 2008). Magnetic resonance imaging also sufficiently defines the anatomy of DOLV (Lilje et al. 2007).

Differential diagnosis may include tetralogy of Fallot or transposition of great arteries with VSD depending on the interrelation of the great arteries. If the aorta is rightward of the pulmonary trunk, tetralogy of Fallot may appear to exist. If the aorta is anterior, transposition of great arteries may appear to exist (Bharati et al. 1978).

Surgical Treatment

Broadly, the aim of surgical correction is direct systemic venous blood into the pulmonary artery and close the VSD (Stegmann et al. 1979) and many treatments have been described based on anatomy (Tchervenkov et al. 2000). Treatments are summarized below according to anatomic considerations (Table 1).

Subaortic VSDs

For patients with subaortic VSDs, surgical treatment depends next on great vessel anatomy. If the pulmonary stenosis is mild in the presence of a subaortic VSD, closure of the VSD with relief of pulmonic stenosis allows for preservation of

Table 1 Double outlet left ventricle biventricular surgical repairs based on coexisting cardiac conditions

VSD	Great vessels	Pulmonary anomaly	Physiology	Repair	Author
Subaortic	Ao rightward of PA	PS	Similar to TOF	Similar to TOF	Bharati et al. 1978; Menon and Hagler 2008
	Ao anterior of PA	Variable PA anatomy	Similar to TGA	RV-PA conduit, pulmonary root translocation	Bharati et al. 1978; Menon and Hagler 2008
	Aorta posterior of PA	Pulmonary atresia		RV-PA conduit	Brandt et al. 1976
	Side by side great arteries	Often PS			Menon and Hagler 2008
	Ao outflow tract obstruction			AP window or DKS with RV-PA conduit	Menon and Hagler 2008
	D-malposed			TOF +/− RV-PA conduit	Menon and Hagler 2008; Brandt et al. 1976; Stegmann et al. 1979
	L-malposed			RV-PA conduit	Stegmann et al. 1979
Subpulmonary or doubly committed	Patent pulmonary outflow tract	None	VSD	VSD closure to connect RV to PA	Brandt et al. 1976; Coto et al. 1979

Complete repair of each condition assumes VSD closure if a VSD is present. *Ao* aorta, *VSD* ventricular septal defect, *PA* pulmonary artery, *PS* pulmonary stenosis, *TOF* tetralogy of fallot, d-*TGA* D-transposition of great arteries, *AP window* aortopulmonary window, *DKS* damus-kaye-stanzel

native outflow tracts. Another option for outflow tract preservation is pulmonary root translocation; however, this is a technically challenging operation (Menon and Hagler 2008). If the aorta is rightward of the PA and pulmonic stenosis is present, a tetralogy of Fallot-type repair may proceed ((Bharati et al. 1978; Menon and Hagler 2008). However, if the great vessels are D-malposed with an anterior aorta, relief of obstruction is difficult or impossible and an RV-PA conduit (Rastelli) is often used (Menon and Hagler 2008; Brandt et al. 1976). When the great vessels are normally related and pulmonary atresia is present, an RV-PA conduit is used (Brandt). In general, if the VSD is near the tricuspid valve, the bundle of His is located along its inferior and posterior edges and is at risk for injury during repair (Tchervenkov et al. 2000).

Aortic Outflow Tract Obstruction

Alternatively, Damus-Kaye-Stanzel procedure with a right ventricle to pulmonary artery conduit may be used (Menon and Hagler 2008). This would commit the patient to either single ventricle physiology or an RV-PA conduit.

Patent Pulmonary Outflow

If pulmonary stenosis is not present, ventricular septal defect closure often proceeds to connect the right ventricle to the pulmonary artery. This closure assumes adequate size of both ventricles (Brandt et al. 1976: Coto et al. 1979). In these cases, the VSD must be subpulmonary, or doubly committed and non-restrictive (Coto et al. 1979).

Single Ventricle

Single ventricle palliation with a Fontan was previously quite rare and employed only in the case of atrioventricular valve atresia (Menon and Hagler 2008). Many children with functionally univentricular hearts are not Fontan candidates and may not even be candidates for surgical palliation (Sharratt 1976; Sakamoto et al. 1997). One case of DOLV with tricuspid atresia was palliated with pulmonary artery banding (Lopes et al. 2001). In another case, Fontan palliation was planned for a child with DOLV and a hypoplastic LV (Alehan and Hallioglu 2003). More recently, single ventricle palliation has been embraced especially for borderline cases in which a suboptimal biventricular repair may be associated with increased surgical mortality (Imai-Compton et al. 2010; Hickey et al. 2009).

Historical Operations

For aortic outflow obstruction, aortopulmonary window creation was palliative. If the ventricular septal defect is subaortic, and pulmonary stenosis could be relieved directly, an intra-atrial baffle directed blood to the pulmonary artery (Brandt et al. 1976). Another antiquated treatment included providing pulmonary blood flow via an intraventricular tunnel repair (Tchervenkov et al. 2000).

To summarize surgical treatment, the VSD is repaired and then the corridor from the right ventricle to the pulmonary artery is constructed as necessary (Bharati et al. 1978).

Postoperative Considerations

In any biventricular repair, the right ventricle has the nascent task of supplying blood to the pulmonary arteries. Consequently, right ventricular function must be supported and preserved (Stegmann et al. 1979). Low cardiac output and cardiac failure often result if the right ventricle does not have suitable preload or function (Brandt et al. 1976).

Outcomes

Successful repair of this lesion may improve New York Heart Association physical status as well as allow for pregnancy (Fukuda et al. 2004).

Patient outcomes characterized with Kaplan-Meier plots for all reported patients with DOLV are reviewed in a single publication by Imai-Compton, et al. which are summarized as follows (Imai-Compton et al. 2010). Survival at 1 year was 75% while 5-year survival was 70%. Biventricular and univentricular repairs had similar survival. Freedom from surgical intervention at age 1 year was only 35% (Imai-Compton et al. 2010). Deaths were attributed to various causes such as genetic syndrome, aortic thrombosis, and myocardial infarction (Imai-Compton et al. 2010). A more recent systematic review by Luciani et al. characterized outcomes of biventricular repair (Luciani et al. 2014). All hospital deaths were due to right heart failure (Luciani et al. 2014). Risk factors for mortality at 1 year were year of operation and outflow patch technique (Luciani et al. 2014) suggesting that modern repairs lead to improved mortality. Ten-year survival was 87% (Luciani et al. 2014). Repair in infancy did not increase mortality (Luciani et al. 2014). Not surprisingly, outcomes appear to have improved over the last 20 years (Luciani et al. 2014).

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Pulmonary Hypertension in Congenital Heart Diseases

Ali Dabbagh and Sepideh Jafari Naeini

Abstract

Pulmonary hypertension (PH) is a severe disease affecting significantly the outcomes of patients with a varying incidence in different studies: from 5 to 52 cases per million population. PH affects many body organs, and is defined as the "progressive disease of the pulmonary vascular system, with a mean pulmonary artery pressure (mPAP) > 20 mmHg at rest measured by right heart catheterization." Concurrent pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg and pulmonary vascular resistance (PVR) of ≤3 Wood units/m^2 are the main indicators of precapillary pulmonary hypertension; after the sixth World Symposium on Pulmonary Hypertension (WSPH) in 2018; the latter defined a new threshold for Pulmonary Hypertension with the rationale that 20 mmHg mPAP is two standard deviations above the normal mPAP (14.0 ± 3.3 mmHg). Currently, the values for mPAP ≥20 mmHg are the same in children above 3 months of age at sea level.

In this chapter, the classification of PH, the clinical diagnosis and management, including the pharmacological agents used in the management of PH, alleviating and aggravating factors in PH, and the role of intravenous sedative and anesthetic agents are discussed in detail.

Keywords

Pulmonary hypertension · Congenital heart diseases · Pediatric

Introduction

Pulmonary hypertension (PH) is a severe disease affecting significantly the outcomes of patients with a varying incidence in different studies: from 5 to 52 cases per million population. PH not only affects many body organs including the heart and lungs but also affects growth and development, especially in children and adolescents (Waxman and Zamanian 2013; Simonneau et al. 2019; Thomas et al. 2020).

Definition

PH is defined as the "progressive disease of the pulmonary vascular system, with a mean pulmonary artery pressure (mPAP) >20 mmHg at rest

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measured by right heart catheterization". Concurrent pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg, and pulmonary vascular resistance (PVR) of ≤3 Wood units/m^2 are the main indicators of precapillary pulmonary hypertension (Nemoto et al. 2019; Simonneau et al. 2019; Thomas et al. 2020); however, this is a new definition from the sixth World Symposium on Pulmonary Hypertension (WSPH) held in 2018. The previous sessions of the WSPH, i.e., from 1973 to 2018, defined mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest in the right heart catheterization as the threshold for PH. However, in the sixth WSPH, the new threshold was defined with the rationale that 20 mmHg mPAP is two standard deviations above the normal mPAP (14.0 ± 3.3 mmHg). It has been also mentioned that the use of specific treatment strategies for pulmonary hypertension in the lower threshold may improve outcomes in systemic sclerosis and chronic thromboembolic pulmonary hypertension (CTEPH) (Hoeper and Humbert 2019). In addition, several studies had demonstrated poor outcomes in patients with mPAP between 20 and 25 (Simonneau et al. 2019; Thomas et al. 2020; Mukherjee and Konduri 2021). Currently, the values for mPAP ≥20 mmHg are the same in children above 3 months of age at sea level (Donti et al. 2007; Ryan et al. 2012; Twite and Friesen 2014; Abman et al. 2015; Low et al. 2015; Simonneau et al. 2019; Thomas et al. 2020; Mukherjee and Konduri 2021). There have been some concerns regarding the acceptable values of PAWP and PVR which have been unchanged in the new definition, and need to be resolved (Jaafar et al. 2019; Thomas et al. 2020).

Classification

Traditionally, PH has been categorized based on the measured values of pulmonary pressure (Forrest 2009; Faqih et al. 2016; Xue et al. 2021; Epstein and Krishnan 2022):

- Borderline PH; 25 mmHg ≥mPAP>20 mmHg.
- Mild PH; mPAP = 25–40 mmHg.
- Moderate PH; mPAP = 41–55 mmHg.
- Severe PH; mPAP>55 mmHg.

In addition, World Conference on Pulmonary Hypertension meeting, supported by the World Health Organization (WHO), has categorized PH under five major groups which are mentioned in Table 1; though there are some overlaps between these groups, especially between the second and the third groups of PH (Friesen and Williams 2008; Ryan et al. 2012; Simonneau et al. 2013; Twite and Friesen 2014; Abman et al. 2015(Epstein and Krishnan 2022).

On the other hand, based on another classification, PH may be classified as precapillary PH and postcapillary PH (Beghetti 2006; Friesen and Williams 2008; Ryan et al. 2012; Ivy et al. 2013; Simonneau et al. 2013, 2019; Twite and Friesen 2014; Abman et al. 2015; Low et al. 2015; Pristera et al. 2016; Oldroyd and Bhardwaj 2021):

Table 1 Classification of pulmonary hypertension (Beghetti 2006; Friesen and Williams 2008; Ryan et al. 2012; Ivy et al. 2013; Simonneau et al. 2013, 2019; Twite and Friesen 2014; Abman et al. 2015; Low et al. 2015; Pristera et al. 2016; Oldroyd and Bhardwaj 2021)

Classification	Definition/title	Pre or postcapillary
Class 1	Pulmonary arterial hypertension (PAH)	Precapillary PH
Class 2	PH due to left-sided heart disease	Postcapillary PH
Class 3	PH due to chronic obstructive lung disease (pulmonary disease)	Precapillary PH
Class 4	PH due to chronic thromboembolic (CTEPH)	Precapillary PH
Class 5	PH because of unclear multifactorial mechanisms	Precapillary PH
		Postcapillary PH (?)

CTEPH chronic thromboembolic pulmonary hypertension

- Precapillary PH: includes groups 1, 3, 4, and 5,
- Postcapillary PH: group 2 is mainly considered the only member of postcapillary PH; however, in some cases group 5 can be categorized as postcapillary PH.

PH due to left heart disease is generally considered the most prevalent form of PH (Mehra et al. 2019). In adult patients, the most common types of PAH according to Anderson et al. are accordingly (Anderson and Nawarskas 2010; Dabbagh 2017):

- Idiopathic/familial PAH is the predominant etiology of PH (40–48%).
- Connective tissue disorders (15–30%).
- Congenital heart abnormalities (11%).
- Portal hypertension (7–10%).
- Anorexigens (3–10%).
- HIV infection (1–6%).

But in recent years, based on the high prevalence of schistosomiasis, it has been introduced as the main cause of PAH in the world (Knafl et al. 2020).

However, in the *pediatric population*, though there are many similarities with adult PH, the frequency rates of PH etiologies differ from adults; pediatric PH is most commonly due to familial type of PH, idiopathic, and neglected or poorly managed congenital heart diseases (PH-CHD), especially when prolonged (Donti et al. 2007; Haworth 2008; Ivy 2016; Kim et al. 2016; Rosenzweig et al. 2019; Abman 2021; Mukherjee and Konduri 2021).

Clinical Features

The main clinical signs and symptoms of PH-CHD include (Friesen and Williams 2008; McDonough et al. 2011; Monfredi et al. 2016):

- Shortness of breath (dyspnea),
- Early fatigability and exercise intolerance,
- Chest pain,
- Syncope or presyncope on exertion,
- Right ventricular heave,
- Ejection click of pulmonary valve,
- Split second heart sound with loud P2,
- A systolic murmur in the tricuspid valve due to tricuspid regurgitation,
- Diastolic murmur due to pulmonary insufficiency,
- Bulged jugular vein,
- Edema and/or ascites.

Paraclinical Studies

Although right heart catheterization is the gold standard for hemodynamic assessment, definitive diagnosis of PH, and deciding on the treatment strategy, several modern sensitive and specific non-invasive imaging modalities have been developed and more are in progress with the special aim to replace these imaging tools instead of pulmonary angiography for diagnosis, management, and follow-up of PH (Lang et al. 2010; Kreitner 2014; Gerges et al. 2015; Pristera et al. 2016).

Chest X-Ray

- Cardiomegaly mainly in the right-sided chambers,
- Elevated cardiac apex due to right ventricle (RV) enlargement and RV hypertrophy,
- Enlargement of the pulmonary artery trunk especially in the outflow tract,
- Decreased retrosternal border in lateral X-ray due to RV enlargement,
- Shrinkage of distal branches of the pulmonary arterial system leading to oligemic lung fields,
- Absence of peripheral branches of the pulmonary artery (pruning).

Electrocardiography (Fig. 1)

- Right axis deviation,
- Right ventricle hypertrophy presenting as R to S wave ratio > 1 in V1,

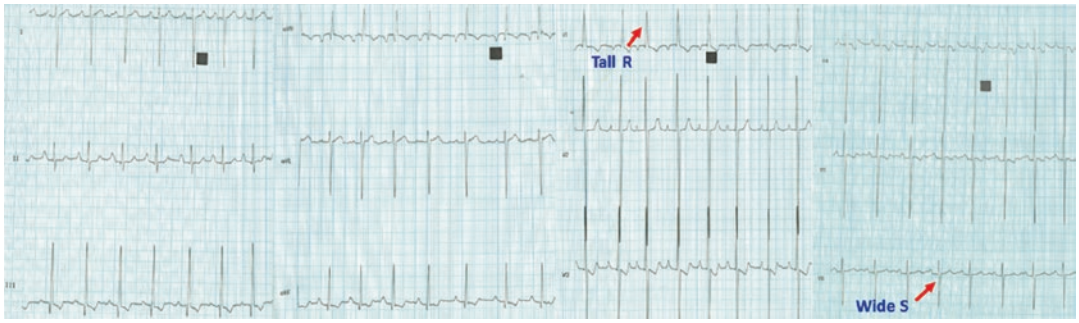

Fig. 1 Right ventricular hypertrophy. Typical ECG features are tall R wave in V1, deep S wave in V6, and right axis deviation. (Courtesy of Dr. Majid Haghjoo and Dr. Mohammadrafie Khorgami)

- Right atrial enlargement presenting as the amplitude of P-wave, especially in lead II,
- Right bundle branch block.

Echocardiography

Evidence of RV hypertrophy and RV enlargement and dysfunction may be seen; pulmonary insufficiency and tricuspid regurgitation may be reported in some patients.

Cardiac MR (CMR) and Multi-Slice CT Scan

Both of them are very important noninvasive imaging modalities and help us perform sophisticated and comprehensive assessments; according to the "Expert consensus statement on the diagnosis and treatment of pediatric pulmonary hypertension" declared in May 2016 by "European Paediatric Pulmonary Vascular Disease Network, endorsed by ISHLT and DGPK" both CMR and CT have a definitive role in pediatric PH; invaluable noninvasive data regarding the right heart and the myocardium as well as the pulmonary vascular system and hemodynamics can be provided by these methods; some believe that parenchymal and vascular assessment of the lungs may be more definitively assessed using CT (Gerges et al. 2015; Santos et al. 2015; Latus et al. 2016).

Radioisotope Ventilation/ Perfusion Scan

It demonstrates the vascular architecture of the lung demonstrating defects and gives structural information about the pathologies that could lead to PH or they can be due to PH (Latus et al. 2016).

Laboratory Tests (BNP/NT-proBNP)

Brain natriuretic peptide (BNP) and N-terminal (NT)-pro Brain natriuretic peptide (NT-proBNP) can be used in screening and risk stratification of pulmonary hypertension with acceptable positive predictive value (Lewis et al. 2020).

Genetic Studies

A genetic consult has been recommended for the following items:

- Presence of a positive family history of pulmonary hypertension (PH)
- In some cases of idiopathic pulmonary artery hypertension (iPAH)
- In the presence of pulmonary capillary hemangiomatosis (PCH)
- Pulmonary veno-occlusive disease (PVOD)
- Hereditary hemorrhagic telangiectasia (HHT)

(Machado et al. 2015; Hernandez-Gonzalez et al. 2020).

Cardiopulmonary Exercise Test (CPET)

Peak V′O2 has been a known predictor of outcomes in pulmonary hypertension, especially in the presence of acceptable results for the 6-min walk test. In addition to Peak V′O2, systolic and diastolic blood pressure at peak exercise, PETCO2 at rest, V′E/V′CO2 slope, and heart rate (HR) at peak exercise can predict the patient's outcomes (Weatherald et al. 2017; Farina et al. 2018).

Definition of PH During Exercise

Although early symptoms of pulmonary hypertension can be manifested during exercise, the definition of pulmonary hypertension during exercise is still under debate. Difficult measurement of hemodynamic parameters such as PAP and PCWP during exercise, absence of a recognized specified pattern of increase in PAP and PCWP in different subgroups (based on the baseline parameters such as age and athletic activities), and inability to distinguish left heart disease from pulmonary vascular disease during exercise-induced PH are some of the remaining issues which should be investigated (Simonneau et al. 2019).

Management

There are some major scopes in the management of children's congenital heart disease associated with PH (Kozlik-Feldmann et al. 2016):

- Definitive criteria should be used for operability and/or starting advanced therapies,
- Preoperative and postoperative management is a great challenge,
- Management of Eisenmenger's syndrome needs sophisticated vigilance and advanced care.

Pharmacological Treatment

The pharmacology of PH for anesthesiologists involves two subclasses: pulmonary vascular system drugs and anesthetic drugs.

A full description of pharmacological agents used for the treatment of pulmonary hypertension could be found in chapter "Cardiovascular Physiology" Cardiovascular Pharmacology in Pediatric Patients with Congenital Heart Disease.

When using pharmacologic agents to treat PH, we should always consider that there are two distinct stages in the treatment of PH

- *Reversible* stage: in this stage, the changes in the pulmonary vascular bed could be partially or near reversed using pharmacologic agents,
- *Irreversible* stage: if the disease progresses, the changes in the pulmonary vascular system are fixed due to permanent vascular bed remodeling and so, the pharmacologic agents are not usually effective.

Except for pharmacologic therapy, other treatment alternatives include "**heart and lung** transplantation" or "**lung transplant** with the repair of the underlying cardiac defect"; however, they are not used in the majority of the patients (Suesaowalak et al. 2010; Liu et al. 2021; Epstein and Krishnan 2022).

The only Food and Drug Administration (FDA)-approved pharmaceutical specifically for the treatment of pulmonary hypertension in children is inhaled nitric oxide (iNO) which is administered through the lungs. The other FDA-approved drugs for the treatment of pulmonary hypertension are used in adults and are often based on the pathways related to the endothelial cells, including prostacyclin analogs (epoprostenol, iloprost, treprostinil), phosphodiesterase 5 inhibitors (sildenafil and tadalafil), phosphodiesterase 3 inhibitors (mainly milrinone), and endothelin receptor antagonist (bosentan, ambrisentan, and macitentan) and Soluble guanylate cyclase stimulator (riociguat) (Benedict et al. 2007; Poor and Ventetuolo 2012; Ventetuolo and Klinger 2014; Abman et al. 2015; Jentzer and Mathier 2015; Liu and Jing 2015; Kim et al. 2016).

Recently, subcutaneous sotatercept, a fusion protein that affects growth pathways, has been successful in reducing pulmonary vascular resistance and N-terminal pro–B-type natriuretic peptide (NT-proBNP) in the population who had

been taking approved medications for PAH with functional class II or III (Fernández-Ruiz 2021; Humbert et al. 2021; Yang et al. 2021; Zolty 2021).

Currently available medications for pediatric PH follow one of the following pathways (Table 2):

1. *Nitric oxide*: It is the only FDA formally approved agent for the treatment of PH in infants and neonates; the others are used in adults and children, they are as off-label drugs; inhaled NO (iNO) increases Cyclic guanosine monophosphate (cGMP), leading to smooth muscle relaxation and subsequently

Table 2 pharmacological agents used in the management of pulmonary hypertension (Anderson and Nawarskas 2010; Ivy et al. 2013; Liu et al. 2013; Abman et al. 2015; Latus et al. 2015; Liu and Jing 2015; Faqih et al. 2016; Hansmann et al. 2016; Kim et al. 2016; Moffett et al. 2016; Dabbagh 2017; Epstein and Krishnan 2022)

Drug	Recommended dose	Adverse effects	Clinical considerations
Inhaled nitric oxide (iNO): Mechanism of action is increasing cGMP, leading to smooth muscle relaxation and subsequently, pulmonary vasodilation			
iNO	2–5 ppm to a maximum of 40 ppm	Lung injury Increased methemoglobin levels Rebound severe pulmonary hypertension due to abrupt iNO withdrawal	The only FDA-approved agent for pediatric pulmonary hypertension Should not be over administered to prevent side effects Its cost may suggest considering the drug as the last choice
Prostacyclin/prostacyclin analogs: Their mechanism of action is pulmonary and systemic vasodilation through increasing cAMP; also, antiplatelet aggregation			
Epoprostenol	*Initial* infusion rate: 1–3 ng/kg/min *Maintenance* infusion rate: 50–80 ng/kg/min	Flushing, headache, nausea, diarrhea, jaw discomfort, rash, hypotension, thrombocytopenia	The potential risk of hypotension and bleeding in children receiving drugs, such as anticoagulants, platelet inhibitors, or other vasodilators
Iloprost	*Initial* dose: 2.5 μg per inhalation; 6 times/day *Maintenance* dose: 5 μg per inhalation 9 times/day	Cough, wheeze, headache, flushing, jaw pain, diarrhea, rash, and hypotension (at higher doses)	The potential risk of exacerbation of reactive airway disease
Treprostinil (IV/subcutaneous)	*Initial* infusion rate: 1.25–2 ng/kg/min *Maintenance* infusion rate: 50–80 ng/kg/min	Flushing, headache, nausea, Diarrhea, musculoskeletal discomfort, rash, hypotension, Thrombocytopenia, and pain at the subcutaneous infusion site	Similar to epoprostenol
Treprostinil (inhaled)	*Initial* dose: 3 breaths (18 μg)/4 times/day *Maintenance* dose: 9 breaths (54 μg) 4 times/day	Cough, headache, nausea, dizziness, flushing, and throat irritation	Reactive airway symptoms and hypotension may occur at high doses
Treprostinil (oral)	*Initial* dose: 0.25 mg PO BID *Maintenance* dose: Determined by tolerability	Headache, nausea, diarrhea, jaw pain, extremity pain, hypokalemia, abdominal discomfort, and flushing	If "twice daily" dosing is not tolerated, consider "three times daily" dosing

Table 2 (continued)

Drug	Recommended dose	Adverse effects	Clinical considerations
PDE-5 inhibitors: Inhibit phosphodiesterase-5, leading to pulmonary vasodilation and inhibition of the vascular remodeling			
Sildenafil	*Oral* dose: 0.25–0.5 mg/kg/q4–8 h *Intravenous* dose: Loading dose 0.4 mg/kg over 3 h Maintenance: Continuous infusion of 1.5 mg/kg/day	Headache, flushing, rhinitis, dizziness, hypotension, peripheral edema, dyspepsia, diarrhea, myalgia, and back pain	Co-administration of nitrates is contraindicated sensorineural hearing loss and ischemic optic neuropathy have been reported
Tadalafil	Oral dose: 1 mg/kg per day (single daily dose): Preliminary studies	Similar to sildenafil No significant effect on vision	Similar to sildenafil
Antagonists of endothelin receptor: Counteract the effects of both endothelin receptors (ET_A and ET_B), vasodilation of the pulmonary vascular system, and vascular remodeling inhibition			
Ambrisentan	Body weight < 20 kg: 2.5–5 mg PO/4 times daily Body weight >20 kg: 5–10 mg PO/4 times daily	Peripheral edema, nasal congestion, headache, flushing, anemia, nausea, and decreased sperm count	Baseline liver enzymes and hemoglobin are needed Monitor based on clinical parameters
Bosentan	2 mg/kg per dose PO, two times daily If body weight is 10–20 kg: 31.25 mg PO, two times daily If body weight is 20–40 kg: 62.5 mg PO, two times daily If body weight is >40 kg: 125 mg PO two times daily	Pediatric abdominal pain, vomiting, extremity pain, fatigue, flushing, headache, lower limb edema, nasal congestion, hypotension, palpitations, dyspepsia, anemia, and decreased sperm count The potential risk of dose-dependent increases in amino-transaminase levels	Liver enzymes and hemoglobin levels should be monitored; in patients with moderate or severe degrees of hepatic impairment, should be used cautiously Also, concomitant use of CYP3A4 inducers and inhibitors should be considered an important caution
Macitentan	10 mg PO, four times daily	Nasal congestion, headache, Flushing, anemia, and Decreased sperm count	The incidence of serum Aminotransferase elevation Is low Obtain baseline Liver enzymes and Hemoglobin and Monitor as clinically Indicated Teratogenicity REMS
sGC stimulator: Its action mechanism is stimulation of soluble guanylate cyclase leading to pulmonary vasodilation associated with inhibition of the vascular remodeling			
Riociguat	*Initial* dose: 0.5–1 mg PO *Maintenance* dose: 2.5 mg PO, three times daily	Headache, dizziness, dyspepsia, nausea, diarrhea, hypotension, vomiting, anemia, gastroesophageal reflux, and constipation	Co-administration of nitrates and/or PDE-5 inhibitors is contraindicated In growing rats, effects on bone formation were observed Teratogenicity is a potential risk Visit www.adempasREMS.com

(continued)

Table 2 (continued)

Drug	Recommended dose	Adverse effects	Clinical considerations
PDE-3 inhibitors: Inhibit phosphodiesterase-3, leading to pulmonary and systemic vasodilation and improved myocardial function			
Milrinone	0.25–0.75 mcg/kg/min Increase/decrease by a minimum of 0.125 mcg/kg/min at intervals no longer than Q 6 h ***Parameters for titration of the drug***: Blood pressure; CO; CI	Arrhythmia, thrombocytopenia, myocardial ischemia, hypotension/vasodilation ***No increase*** in myocardial oxygen demand	May increase heart rate No risk of myocardial ischemia Increases cardiac output Risk of arrhythmia

pulmonary vasodilation. iNO is transported very fast through the alveolar-capillary membranes and then rapidly metabolized by circulating erythrocytes; all in just a few seconds; so, iNO is an ideal drug; inhalation is the best-targeted therapy in PH with the least systemic side effects. iNO dose starts from 2 to 5 ppm to a maximum of 40 ppm through the endotracheal tube, face mask, or nasal cannula with specific delivery instruments; higher doses are both ineffective and may cause side effects like lung injury and/or increased methemoglobin levels; iNO should ***not*** be withdrawn abruptly, or there would be severe rebound PH (Latus et al. 2015; Kim et al. 2016; Moffett et al. 2016). In the "2019 updated consensus statement on the diagnosis and treatment pulmonary hypertension (PH)," iNO has been recommended for:

- Treatment of PH in children in the presence of parenchymal/interstitial lung disease
- Premature infants below 34 weeks of gestation with documented PH
- Some cases of persistent pulmonary hypertension of the newborn (PPHN)
- Occasionally in post-operative PH (Hansmann et al. 2019).

2. *Endothelin-receptor antagonists*: They are effective in the treatment of ***mild*** to ***moderate*** PH; they include ambrisentan, bosentan, and macitentan; these agents counteract the effects of both endothelin receptors (ET_A and ET_B), leading to vasodilation in the pulmonary vascular system, and also, inhibit vascular remodeling. Bosentan inhibits both ET_A and ET_B, lowering PAP and PVR and improving exercise tolerance. Bosentan is approved for use in children over 12 years in the US and children over 3 years in Canada. Hepatic function should be monitored seriously when administrating bosentan. The bosentan dose is:
   (a) 10–20 kg: Initial: 31.25 mg once daily for 4 weeks; increase to the maintenance dose of 31.25 mg twice daily
   (b) >20–40 kg: Initial: 31.25 mg twice daily for 4 weeks; increase to the maintenance dose of 62.5 mg twice daily
   (c) >40 kg: Initial: 62.5 mg twice daily for 4 weeks; increase to the maintenance dose of 125 mg twice daily (Allen et al. 2013; Liu et al. 2013).
3. *Prostacyclin system analogs* (epoprostenol, iloprost, beraprost, treprostinil "IV/subQ/inhaled/oral): These are effective in the treatment of moderate-to-severe PH; they cause pulmonary and systemic vasodilation through

increasing cAMP; also, they have antiplatelet aggregation effects; they have very short onset of effect; so, they act very rapidly and have a short half-life. *Epoprostenol* is the most widely studied agent which is given through continuous IV infusion; for epoprostenol central venous line may be needed and one should be cautious not to discontinue the infusion even during insertion of a CV line. *Iloprost* is the inhaled analog with clinical effects similar to iNO. *Treprostinil* is the analog that could be used subcutaneously or IV; and finally, *Beraprost* is another analog used orally (Friesen and Williams 2008; Twite and Friesen 2014; Kim et al. 2016; Moffett et al. 2016).

4. *Phosphodiesterase 5 (PDE-5) inhibitors*: They, mainly sildenafil and tadalafil, and at times, vardenafil, lead to pulmonary vasodilation and inhibition of vascular remodeling. PDE 5 degrades cGMP and when inhibited, accumulation of PDE 5 in smooth muscles of the pulmonary system leads to pulmonary vasodilation (both in acute and chronic PH). Sildenafil is available both in oral and intravenous forms, but should be used with extreme caution to prevent life-threatening hypotension. In European Union, sildenafil has been approved for patients between 1 and 17 years. However, in the US, there are still some concerns, especially when iNO is available. The oral dose of sildenafil is 0.25–0.5 mg/kg each 4–8 h; with a maximum dose of 2 mg/kg every 4 h; titration of the dose should be based on clinical response; the intravenous dose could be found in Table 2. These data are in large the same for tadalafil, except for its does which is found in Table 2 (Shah and Ohlsson 2011; Beghetti et al. 2014; Vorhies and Ivy 2014; Wang et al. 2014; Dodgen and Hill 2015; Perez and Laughon 2015; Lakshminrusimha et al. 2016; Liu et al. 2021; Epstein and Krishnan 2022).
5. *PDE-3 inhibitors*, mainly milrinone, have positive inotropy and arterial dilation effects with weak chronotropic effects so an "***inodilator.***" They inhibit PDE-III isoenzyme in cardiomyocytes and vascular smooth muscle cells; so, intracellular cAMP levels are peaked up which in turn, leads to increased protein kinase A (PKA). With increased PKA, contractile elements of cardiomyocytes are activated. In smooth muscle cells of the arterial system, PKA leads to relaxation of the vessel wall. Dose and adverse effects are presented in Table 2 (Knight and Yan 2012; Ferrer-Barba et al. 2016).
6. *sGC stimulator* or soluble guanylate cyclase stimulator (riociguat): It acts through stimulation of soluble guanylate cyclase causing pulmonary vasodilation and also, inhibits vascular remodeling (Benedict et al. 2007; Suesaowalak et al. 2010; Poor and Ventetuolo 2012; Ventetuolo and Klinger 2014; Abman et al. 2015; Jentzer and Mathier 2015; Kim et al. 2016),
7. Selective IP prostacyclin-receptor agonist: Selexipag, in oral form in adults, has been previously studied in the GRIPHON trial in 2015 with remarkable outcomes. Recently its safety in children has been evaluated in trials with acceptable results for selexipag in children (Sitbon et al. 2015; Faqih et al. 2016; Epstein and Krishnan 2022).

Anesthesia for Patients with Congenital Heart Disease and Pulmonary Hypertension

The anesthesiologists dealing with PH-CHD patients should keep in mind the ideal goals of the treatment which include prevention of any unnecessary manipulations (for example avoiding Pulmonary Artery Catheter insertion), preserving

the function of the heart and preventing any imbalance in interventricular shunts, and if possible, implement pulmonary vasodilating strategies.

The ideal anesthesia should fulfill the following goals in patients with PH-CHD

- Pulmonary vasodilating effect (i.e., decreasing PVR).
- Preserving cardiac contractile function, cardiac function, and systemic vascular resistance (i.e., maintaining CO and SVR).
- Short-acting and easily titratable.

The anesthesia management should be done with great caution with prevention of any provoking agent and administering alleviating measures which are an integral part of treatment in PH, especially during acute attacks; these counteracting measures are described briefly in Table 3 based on some of the international guidelines and reviews.

The anesthetic agents used for these patients are described in brief in Tables 4 and 5. In general, an anesthetic regimen could include a selected combination of these agents (Friesen and Williams 2008; Galante 2011; Twite and Friesen 2014; Epstein and Krishnan 2022):

- Isoflurane and sevoflurane.
- Fentanyl.
- Midazolam.
- Etomidate.
- Propofol.
- Ketamine (with major controversies for PH).

Table 3 Alleviating and aggravating factors in PH (Friesen and Williams 2008; Galante 2011; Ivy et al. 2013; Twite and Friesen 2014; Abman et al. 2015; Dabbagh 2017; Rosenzweig et al. 2019; Abman 2021; Epstein and Krishnan 2022)

Provoking agents or aggravating factors	Alleviating measures
• Hypoxia • Hypotension • Acidosis • Pain • Forceful and/or harsh tracheal intubation • Deep tracheal suctioning • Hypoventilation • Hypercarbia	• 100% O_2 • Modulating cardiac output • Correction of hypotension and hypoxia • Hyperventilation to induce respiratory alkalosis • ***Avoiding*** extra pressure during ventilation, since it will overcome the "blood pushing pressure" in the pulmonary vascular system • Pulmonary vasodilators • Treatment of acidosis • Using appropriate and titrated anesthetic agents • Using analgesics like fentanyl augmenting SVR to overcome PVR using vasodilators; there should be appropriate pulmonary/systemic pressure and any underlying right to left shunt be prevented; phenylephrine and epinephrine should be used if needed to augment SVR • ECMO may be needed to support perfusion

Table 4 Intravenous sedative and anesthetic agents (Dabbagh 2017)

Medication	Mechanism of action	Dosing	Indication	Adverse events and specific clinical considerations
Propofol	Modulation of $GABA_A$ receptor complex	Bolus: 1–3 mg/kg Infusion: 100–200 μg/kg/min for procedural sedation	Procedural sedation	Do not use for prolonged sedation>4 h (risk of propofol infusion syndrome) Risk of cardiac output drop
Midazolam	Modulation of $GABA_A$ receptor complex	Infusion: 0.025–0.1 mg/kg/h average: 0.05–0.1 mg/kg/h	Amnesia, sedation, anxiolysis	Rapid tolerance with an infusion Onset: 1–5 min Duration: 20–30 min
Lorazepam	Modulation of $GABA_A$ receptor complex	Bolus: 0.025–0.1 mg/kg q 4 h Infusion:0.025 mg/kg/h	Amnesia, sedation, anxiolysis	Risk of tolerance with an infusion Onset: 1–5 min Duration: 20–30 min
Dexmedetomidine	Synthetic central α2 agonist (purely α2; vs. clonidine)	0.3–0.7 μg/kg/h	Sedation; some analgesia	For short-term ICU sedation; Bradycardia and heart block in Infants Half-life: 6–12 min
Clonidine	α1 and α2 adrenoceptor agonist (90% α2 with some α1 activity)	Infusion: 0.25–1 μg/kg/h	Analgesia, sedation	Does not cause significant respiratory depression May lead to hypotension
Etomidate	Modulation of $GABA_A$ receptor complex	Children >10 years of age: 0.3 mg/kg (0.2–0.6 mg/kg)0.1	Sedation	Onset: 1 min Duration:3–5 min
Ketamine	NMDA receptor antagonist	Bolus: 1.5–2 mg/kg May administer incremental doses of 0.5–1 mg/kg every 5–15 min as needed	Analgesia, sedation	Hallucinations Increased pulmonary pressure Dysphoria Excessive salivation Tachycardia Onset: 3–5 min duration: 20–30 min

Table 5 Volatile anesthetics (Dabbagh 2017)

Drug	MAC Value %	Comments
Isoflurane	1.6 (newborn) 1.87 (1–6 months) 1.8 (0.5–1 year) 1.6 (1–12 years)	Irritates the respiratory tract, which may lead to ***laryngospasm*** in children
Sevoflurane	3.3 (newborn) 3.1 (1–6 months) 2.7 (0.5–1 years) 2.55 (1–12 years)	A good choice for mask induction in pediatric anesthesia Decreases the chance of postoperative nausea and vomiting Shortened recovery time and more rapid recovery of perception, which might produce a state of restlessness
Desflurane	9.2 (newborn) 9.4 (1–6 months) 9.9 (0.5–1 years) 8.0–8.7 (1–12 years)	***Not suitable*** for ***mask*** induction in pediatric anesthesia because of its pungent smell, respiratory tract irritation, apnea, and laryngospasm

MAC minimum alveolar concentration

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Right Ventricular Failure

Yamile Muñoz and Renzo O. Cifuentes

Abstract

Perioperative right ventricular (RV) failure is a complication associated with significant risk and an increase in the morbidity and mortality of patients.

Thorough knowledge of the anatomy and the complex physiology of the normal right ventricle (RV) is crucial to advance in the diagnosis and management of this syndrome. It is important to understand when the RV is underperforming because early intervention allows us to determine the precipitating events and prevent further deterioration.

One must review the anatomical and physiologic characteristics of the normal RV, the pathophysiology of RV failure, and the management recommendations.

Keywords

Right ventricle · Right ventricular failure Right ventricle dysfunction · Ventricular interdependence · Pulmonary vascular resistance

Abbreviations

BP	Blood pressure
CHD	Congenital heart disease
CO	Cardiac output
CRVF	Chronic right ventricular failure
CVP	Central venous pressure
ECMO	Extracorporeal membrane oxygenation
EDP	End-diastolic pressure(s)
iNO	Inhaled nitric oxide
IVS	Interventricular septum
LV	Left ventricle
LVAD	Left ventricular assist device
MCS	Mechanical circulatory support
ME	Mid-esophageal
PAP	Pulmonary artery pressure
PDE	Phosphodiesterase
PH	Pulmonary hypertension
PVR	Pulmonary vascular resistance
RV	Right ventricle or right ventricular
RVAD	RV assist devices
SV	Stroke volume
SVR	Systemic vascular resistance
TEE	Transesophageal echocardiography
TG	Transgastric
TR	Tricuspid regurgitation
TTE	Transthoracic echocardiography
VA-ECMO	Veno-arterial ECMO
VV-ECMO	Veno-venous ECMO

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Anatomy and Physiology of the Right Ventricle

Compared to the left ventricle (LV), the myocardium of the right ventricle (RV) is thin, it is 1–3 mm thick, while its counterpart (LV) on its free wall is 10 mm. In a transverse cut, we can appreciate the complex geometrical shape of the RV, which has a crescent shape, while, the LV, on the other hand, has a circular shape. The free wall of the RV forms the anterior border of the heart and the other half is part of the interventricular septum (IVS) (Fig. 1a).

The right ventricular wall is made out of a superficial layer of oblique fibers that continue with the superficial myofibers of the LV, and a deep layer of muscular fibers longitudinally aligned (Haddad et al. 2008a).

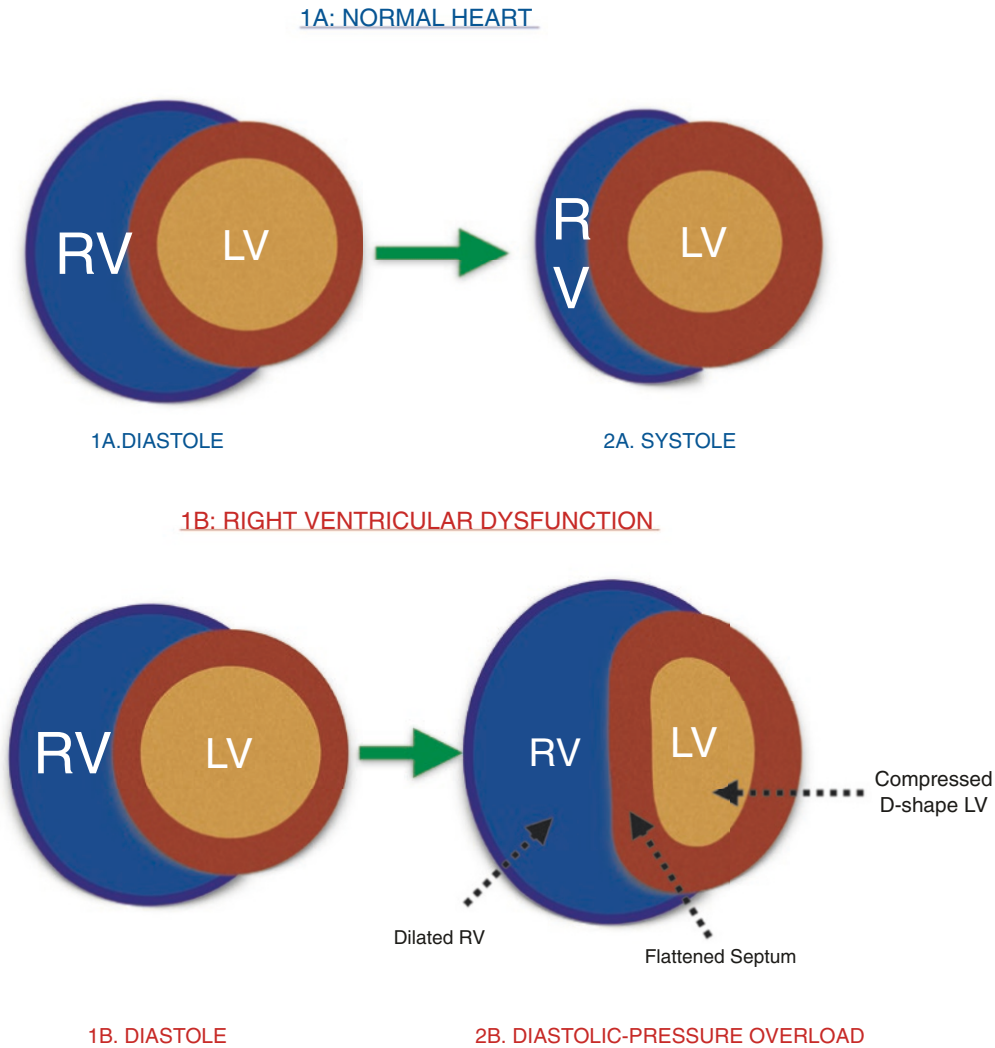

Fig. 1 1A,2A: Represents the normal morphology of the RV and LV in systole and diastole. 1B,2B: Represents ventricular interdependence in RV dysfunction. There is significant pressure elevation in the RV during both systole and diastole, resulting in dilation of the RV, flattening of the interventricular septum and compression of the LV that resembles a D shape (D-shape LV). This leads to a decrease in LV compliance leading to further increase in afterload

The normal contraction of the RV resembles a peristaltic movement that begins at the inflow tract, through the apical trabeculated portion, and through the infundibulum. The normal ejection from the RV is due to the longitudinal shortening of the free wall as well as a reduction in the distance between the septum and the free wall causing a below effect. Under normal conditions, the LV contributes to 20 to 40% of the RV's contractile function.

RV perfusion happens in both systole and diastole, making it less susceptible to ischemia than the LV.

With these anatomical bases, we can see the relationship between the two ventricles and deduce that RV pathology can affect the LV and vice versa through a phenomenon called ventricular interdependence. Furthermore, the relationship between volume over ventricular mass gives the RV high compliance which allows it to manage greater volumes with minimal increase of the intracavitary pressure (Greyson 2008; Haddad et al. 2008a).

There are two fundamental aspects of RV physiology.

The first is that it is characterized by high compliance that can accommodate large variations in venous return without a high impact on the end-diastolic pressure (EDP). We can make this assumption by observing a pressure-volume curve comparing the two ventricles, where we will see that the triangular shape of the RV is less steep during its diastolic phase than the LV's (Haddad et al. 2008b; Vandenheuvel et al. 2013).

Second is that the RV physiology is highly dependent on the afterload; slight elevations of the pulmonary vascular resistance (PVR) lead to a marked reduction in its systolic function. In Fig. 2, we can observe the effect of afterload on stroke volume (SV) compared to both RV and LV. For every increase in the afterload, the decrease in the SV is greater in the RV than in the LV (Haddad et al. 2008a).

The RV is attached to the pulmonary vascular bed that is a high flow and low resistance system; it is of low resistance because the pulmonary arterioles have a thin media layer and few smooth muscle cells, making them very elastic, with a greater capacitance and capable of handling volume when recruited (Haddad et al. 2008b; Greyson 2012).

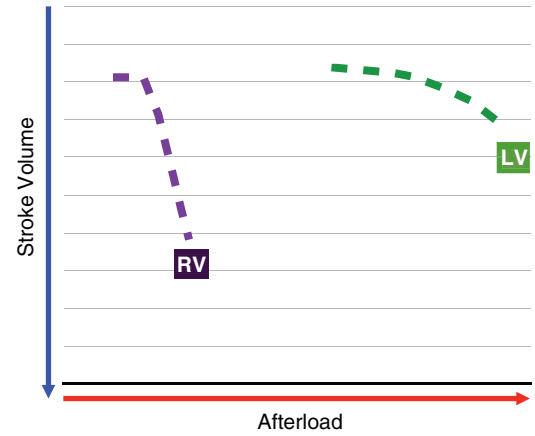

Fig. 2 Effect of afterload on Stroke Volume (SV) compared on both RV and LV

Even though the RV afterload is determined by many factors (PVR, distensibility of the pulmonary arterial system, and a dynamic component called Inductance), PVR remains the most commonly used index to determine RV afterload (Price et al. 2010).

Pulmonary vascular tone is predominantly controlled by the vascular endothelium, and by balanced production of vasodilators (prostacyclin, nitric oxide) and vasoconstrictors (endothelin 1, thromboxane A2, and serotonin). PVR is defined as the mean pulmonary arterial pressure (mPAP) minus pulmonary artery occlusion pressure (PAOP that provides an indirect measure of the left atrial pressure) divided by the cardiac output (CO). The normal range is between 30 and 180 dynes/s/cm^{-5} or less than 2 Wood units.

$$\mathrm{PVR} = 80 \times \left(\mathrm{mPAP} - \mathrm{PAOP}\right) / \mathrm{CO}$$

This formula shows us very important details about cardiac physiology:

1. PVR can be affected by an increase in the left atrial (LA) pressure; this can be due to diastolic, systolic, or mixed dysfunction of the LV and/or mitral disease (stenosis or regurgitation).

2. CO disorders can increase PVR; this is the case of congenital heart disease (CHD) with a left to right shunt, fluid overload, or hyperdynamic states.
3. The lungs and the heart are linked together very closely and their interaction is very important for normal physiology. A disruption in the lungs can lead to an increase in PVR, e.g., interstitial lung disease, and pulmonary embolism (PE) (Zochios and Jones 2014).

Definition

RV failure is defined as a clinical syndrome resulting from the inability of the RV to maintain an adequate blood flow to the pulmonary circulation in the setting of adequate preload, which progressively will lead to systemic hypoperfusion (Haddad et al. 2008b; Zarbock et al. 2014; Grant et al. 2021).

Etiology

It can be divided based on the pathophysiology and there are several perioperative factors that can alter these three elements of the CO:

1. **Volume overload**. The volume overload is caused by conditions such as tricuspid regurgitation (TR), atrial septal defects (ASD), and ventricular septal defects (VSD). A very important cause of volume overload in the perioperative setting is excessive administration of intravenous (IV) fluids. Based on what was discussed about the anatomical and physiologic characteristics, the RV can accommodate more easily volume overload with a relatively low increase in the wall tension. Therefore, chronic volume overload is well tolerated but puts the patient at risk of acute decompensation because a chronically overloaded RV has a limited capacity of increasing its contractility in the event of an acute increase of PVR.
2. **Reduced contractility**. The contractility can be affected by myocardial ischemia due to coronary artery disease or a decrease in the perfusion pressure due to hypotension, arrhythmias, intrinsic myocardial diseases such as cardiomyopathies, or cytokine-induced myocardial depression like sepsis. In observational studies, up to 40% of patients with sepsis have evidence of RV failure due predominantly to primary RV dysfunction (Itagaki et al. 2012).
3. **Pressure overload**. Pressure overload is the most common cause of systolic dysfunction of the RV (Vandenheuvel et al. 2013; Greyson 2012). PVR increases by perioperative factors like:
   (a) Pulmonary vasoconstriction is secondary to severe hypoxia, hypercapnia, acidosis, cytokine release due to blood transfusion, protamine, hypothermia, pain, and stress.
   (b) Reduction or compression of the pulmonary vascular bed induced by acute respiratory distress syndrome (ARDS), PE, pneumothorax, ventilation with large tidal volumes, high plateau pressures, and high positive end-expiratory pressures (PEEP).
   (c) Congestion of the pulmonary vascular bed in case of pulmonary hypertension (PH) secondary to valvular disease or chronic obstructive pulmonary disease (COPD), and LV failure that results in a retrograde increase of pulmonary artery pressure (PAP).
   (d) Mechanical obstruction as in pulmonary stenosis or RV outflow tract obstruction.

RV dysfunction is present in many critically ill patients. The incidence of acute RV failure in patients with ARDS is around 60% without protective mechanical ventilation and 25% with protective mechanical ventilation (Grant et al. 2021). Postoperative RV failure is around 0.1% in patients post-cardiotomy, 2–3% after a cardiac transplant, 25% in CHD repair patients, and 30% after the implantation of an LV ventricular assist device (LVAD) (Krishnan and Schmidt 2015). In

patients with PE, the echocardiographic findings of RV dysfunction can be present in 29–56% of the cases (Krishnan and Schmidt 2015). The presence of RV failure is an independent predictor of mortality.

Table 1 describes the causes of RV failure.

Table 1 RV dysfunction etiologies

Preload	
Low	• Hypovolemia (e.g., third spacing, copious urine output)
	• Tamponade
High	• Fluid overload
	• Left to right shunting (e.g., PFO, ASD, VSD, PDA)
	• Valvular disease: tricuspid regurgitation, pulmonary regurgitation
Contractility	
Decreased inotropism	• Preexisting RV dysfunction due to CAD or valvular disease
	• Myocardial stunning after Cardiopulmonary Bypass (CPB)
	• Poorly protected myocardium
	• Post-cardiotomy
Arrythmias	• Atrial fibrilation, SVT and VT
Hypoperfusion	• RCA occlusion
	• RCA thromboembolism
	• RCA air embolism
	• Hypoperfusion secondary to LV dysfunction
	• Mechanical obstruction or kinking of RCA or graft
Afterload	
Mechanical obstruction	• RVOT obstruction
	• Pulmonary stenosis:
	– Valvar
	– Subvalvar
	– Supravalvar
	• Anastomotic stenosis
	• Pulmonary veno-occlusive disease (PVOD)
Pulmonary vasoconstriction	• Hypoxia
	• Hypercarbia
	• Acidosis
	• Blood transfusions
	• Drugs
	– Protamine
Congestion of the pulmonary vascular bed	• Preexisting PHTN due to valvular disease and COPD
	• Postoperative LV dysfunction
Compression and/or reduction of the pulmonary vascular bed	• Pulmonary embolism
	• Pneumothorax
	• Acute lung injury or ARDS
	• Positive pressure mechanical ventilation with high PEEP

PFO patent foramen ovale, *ASD* atrial septal defect, *VSD* ventricular septal defect, *PDA* patent ductus arteriosus, *LV* left ventricle, *RV* right ventricle, *CPB* cardiopulmonary bypass, *SVT* supra-ventricular tachycardia, *VT* ventricular tachycardia, *CAD* coronary artery disease, *RCA* right coronary artery, *RVOT* right ventricular outflow tract, *PVOD* pulmonary veno-occlusive disease, *PHTN* pulmonary hypertension, *COPD* chronic obstructive pulmonary disease, *ARDS* acute respiratory distress syndrome, *PEEP* positive end expiratory pressure

Pathophysiology

The first response to an acute rise of RV overload is an increase in ventricular contractility, which is mediated through rapid alterations in intracellular calcium dynamics and is known as the Anrep effect.

As the pulmonary impedance increases, the sympathetic nervous system is activated releasing catecholamines which allow an increase in the pressures of the RV by increasing inotropism. If the PVR continues to increase, the RV dilates and the systolic volume is maintained by the Frank-Starling mechanism since an increase in the end-diastolic volume of the RV increases contractility.

Once the ventricle reaches its limit of the compensatory reserve, a greater increase in the afterload can induce a sudden hemodynamic collapse.

We must highlight three points in regard to a sudden hemodynamic collapse due to RV failure:

1. The decrease in CO is a consequence of the ventricular interdependence; the dilation of the RV deviates from the IVS to the left decreasing LV compliance which in a retrograde fashion increases the RV's afterload furthermore (Fig. 1b).

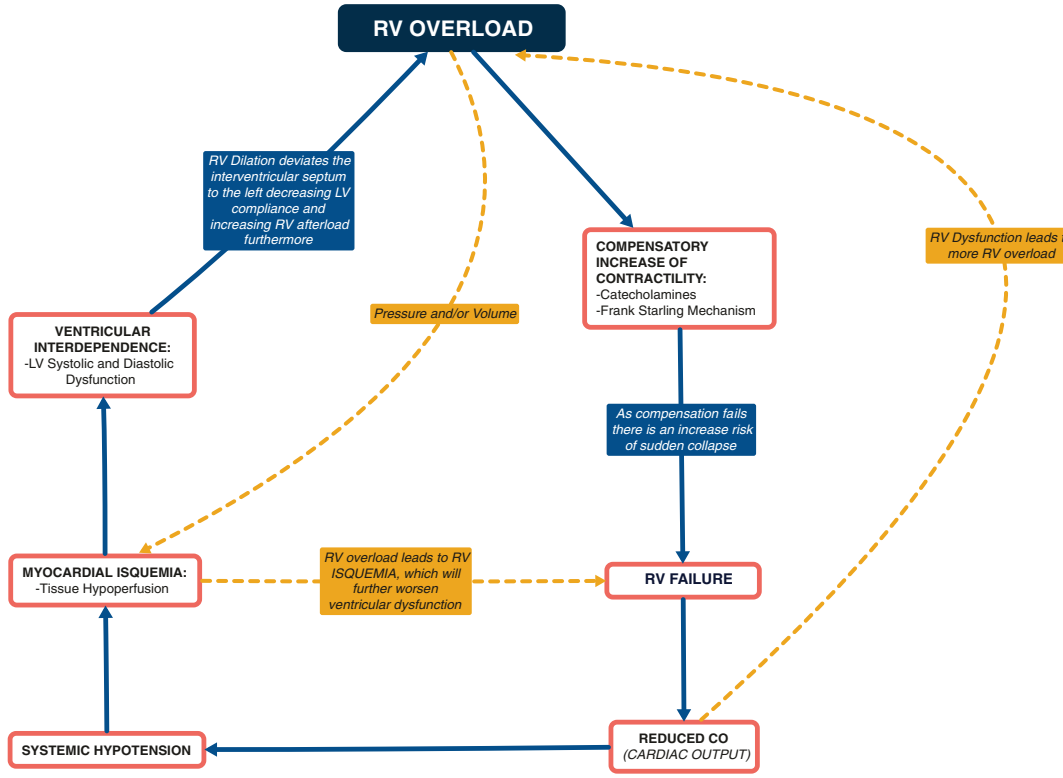

Fig. 3 Pathophysiology of RV failure. RV overload induces an initial compensation by increasing contractility (catecholamines release and the Frank Starling mechanism). Compensation eventually fails and RV failure will be stablished. RV failure reduces CO, which will result in systemic hypotension that causes myocardial ischemia and tissue hypoperfusion. RV failure itself will induce more RV overload. RV ischemia worsens RV failure. RV failure causes RV dilation that will deviate the interventricular septum towards the left, decreasing LV compliance and increasing RV afterload furthermore, this is due to ventricular interdependence. LV systolic and diastolic dysfunction leads to more RV overload worsening RV failure

2. The sustained increase in the PVR.
3. The hemodynamic collapse is the RV ischemia secondary to a decrease in the blood pressure (BP) which affects the contractility even more.

This is how we enter a vicious cycle in which the RV dysfunction per se generates more RV failure and we go down a spiral of progressive ischemia, increased PVR, and shock (Fig. 3).

Diagnosis

Clinical signs of RV dysfunction are unspecific and could be shared with other pathologies, especially in critically ill patients.

High suspicion should be held in the postoperative patients of CHD mainly those with interventions on the RV and/or concomitant PH.

On physical exam, mainly in the chronic patient, it is common to find jugular ingurgitation, hepatomegaly, liver pulsation, peripheral edema, and a right-sided third heart sound (S3) or systolic murmur from TR.

In the critically ill or postoperative congenital cardiac surgery patient, it is characterized by the presence of systemic hypotension, elevated central venous pressure (CVP), decreased oxygen saturation, and tissue hypoperfusion in severe cases.

As the clinical signs of acute RV, failure are nonspecific, point-of-care cardiac ultrasound (POCUS) has become particularly important for

detecting acute RV dysfunction, guiding specific therapies, and monitoring the impact of care on the recovery or deterioration of the RV.

At this point, it is important to mention that the measurement of CO using the method of thermodilution with a pulmonary artery catheter can be altered in the presence of TR secondary to dilation of the RV making it difficult to assess the response to the medical management, though it remains the standard method to evaluate PAP and PVR. The pulmonary artery catheter and the bedside cardiac echocardiogram focused on a qualitative assessment of global and segmental RV function can be used complementary in the diagnosis and follow-up of the patient with RV failure to guide the impact of supportive therapies.

Echocardiographic Evaluation of the RV

The echocardiogram plays an important role in the diagnosis of RV dysfunction.

In the cardiac surgery intraoperative setting, the transesophageal echocardiogram (TEE) is the preferred modality; however, in the critically ill patient transthoracic echocardiogram (TTE) gives good image quality for bed-side evaluation of RV function, RV size, and load condition. For the assessment of the RV, it is important to keep in mind its complex three-dimensional geometry, but the use of focused cardiac ultrasound is an accurate, rapid, and reproducible bedside test. Through the apical four-chamber and subcostal views, it is possible to qualitatively estimate the RV contractility, RV dimension (normally one-third of the LV), and the presence of a D-shaped LV, and to rule out extrinsic causes of RV failure as tamponade or other causes of hemodynamic compromise.

The American Society of Echocardiography and the European Association of Cardiovascular Imaging published guidelines for the quantitative assessment of global RV function and recommend the use of the following echocardiographic parameters (Lang et al. 2015; Table 2):

1. *RV fractional area change (RVFAC)*: It is the ratio of the change in the RV end-diastolic area to the RV end-systolic area (RVED area − RVES area)/RVED area. When tracing the area of the endocardial border, the trabeculations and papillary muscles should be included in the RV cavity. It is a global measure of RV systolic function and has been shown to correlate with RV ejection fraction measured by MRI and 3D echo (Imada et al. 2015). Normal values are ≥35% (Lang et al. 2015), and values <17% represent severely decreased RV systolic function. It can be obtained on TEE in the ME four-chamber view and on TTE in the apical four-chamber view. Measurements of RVFAC using these

Table 2 Echocardiographic parameters for RV function

Parameters	TTE	TEE	Abnormal values
1. RV:LV area ratio	Apical four chamber	ME four chamber	>0.6
2. RV fractional area change	Apical four chamber	ME four chamber	<35%
3. LV eccentriciy index	Parasternal midpapillary short axis	TG midpapillary short axis	>1
4. TAPSE[a]	Apical four chamber	Deep TG RV	<17 mm
5. TAPSV[b]	Apical four chamber	Deep TG RV	<9.5 cm/s
6. Myocardial performance index	Apical four chamber	Deep TG RV	>0.4 by pulsed Doppler
			>0.55 by tissue Doppler
7. RV longitudinal free wall strain	RV focused four chamber	ME four chamber	>−20%

ME midesophageal, *TG* transgastric, *RV* right ventricle, *LV* left ventricle
[a] TAPSE: tricuspid annular plane systolic excursion
[b] TAPSV: tricuspid annular plane systolic velocity

techniques do not vary significantly (Vandenheuvel et al. 2019).

2. *LV eccentricity index*: Normally, the IVS is curved towards the RV (Fig. 1b). When the RV is compromised, the IVS deviates to the left making a D-shaped LV. The eccentricity index is a quantification of this phenomenon, and it is defined as a ratio of two perpendicular diameters of the LV cavity in the short-axis view (the anteroposterior and septolateral). It can be obtained on TEE in the TG mid-papillary short-axis view and on TTE parasternal short-axis view and its normal value is 1. If this relationship is greater than 1 (>1), it means that the RV is exposed to either pressure or volume overload. If the eccentricity index predominates in systole, it means pressure overload, on the contrary, if it predominates in diastole, it means volume overload (Zaidi et al. 2020a).
3. *Tricuspid Annular Plane Systolic Excursion (TAPSE)*: It is a measure of the longitudinal motion of the RV free wall. TAPSE is acquired by placing an M-mode cursor through the lateral aspect of the tricuspid annulus and measuring the distance traveled from the end of diastole to the end of systole. It is obtained on an apical four-chamber view using TTE. TAPSE measured in the ME four-chamber view on TEE can substantially underestimate TAPSE measured in the apical four-chamber view on TTE. For this reason, it is recommended that, to acquire TAPSE on TEE, place the M-mode cursor through the tricuspid annulus on a deep TG of the RV inflow view or use a modified deep TG view focusing on the right ventricle, trying to align the probe as vertically as possible to the apex of the heart (Vandenheuvel et al. 2019). However, TAPSE by M-mode in the deep TG RV inflow and modified TG view can also underestimate the TAPSE compared to M-mode in the apical four-chamber view (Flo Forner et al. 2017; Korshin et al. 2018). Reasons for persistent underestimation include misalignment and visualization of a less mobile part of the tricuspid annulus. Although TAPSE is a regional measure, it correlates with global RV systolic function and clinical outcomes (Rudski et al. 2010). A TAPSE <17 mm is indicative of RV dysfunction. In cardiac surgery, clinicians should be aware that measurements of TAPSE on TEE are not interchangeable with those made by cardiologists in the echo lab before induction of anesthesia. Alternative technologies like TAPSE by anatomic M-mode, speckle tracking-based TAPSE, or measuring the distance from the tricuspid annulus to the apex in end-systolic and end-diastolic frames (modified TAPSE) are promising (Zochios and Jones 2014; Krishnan and Schmidt 2015; Morita et al. 2016). In mechanically ventilated patients as occurs in the intensive care unit, the apical echocardiographic window could have limitations. A novel approach using subcostal inferior vena cava view and using M-mode to measure excursion of the tricuspid annulus has emerged. Subcostal echocardiographic assessment of tricuspid annular kick (SEATAK) has demonstrated a good correlation with TAPSE measurements by TTE with a mean pairwise difference of −0.26 cm and could be an excellent option in this group of patients (Díaz-Gómez et al. 2017). TAPSE could be used as a follow-up parameter in patients with RV failure to asses evolution and response to treatment.
4. *RV/LV area ratio*: It is measured at the end of diastole by tracing the areas of the two chambers in the apical four-chamber view on TTE or the mid-esophageal (ME) four-chamber view on TEE. A ratio of 0.6 suggests moderate RV dilation, whereas a ratio of 1.0 indicates severe RV dilation.
5. *Tricuspid Annular Plane Systolic Velocity (TAPSV)*: It is the Doppler tissue imaging-derived systolic S′ velocity of the tricuspid annulus. It is obtained by placing the sample volume at the tricuspid annulus or the middle of the basal segment of the RV free wall in the apical four-chamber view on TTE and on a deep TG of the RV on TEE, then the peak systolic velocity (S′) is determined. TAPSV has

not been studied extensively in TEE and similarly to TAPSE, this technique can underestimate the measurement compared with a cardiologist's measurement before induction of anesthesia. The main advantage compared to TAPSE is to be less dependent on loading conditions (Vandenheuvel et al. 2019). A value <9.5 cm/s is an indicator of RV dysfunction (Lang et al. 2015).

6. *Myocardial Performance Index (RVMPI or Tei Index)*: It is defined as the sum of isovolumetric contraction time and isovolumetric relaxation time divided by ejection time and represents a global estimate of both systolic and diastolic function of the RV. It can be obtained using either the pulsed Doppler or tissue Doppler method on an apical four-chamber view using TTE or on a deep TG of the RV on TEE. The tissue Doppler method has the advantage that all time intervals are measured from a single beat placing the sample volume on the tricuspid annulus. When the pulsed Doppler method is used, these time intervals are measured from tricuspid inflow and right ventricular outflow, so one should use beats with similar R-R intervals to be more accurate (Rudski et al. 2010). A value >0.4 using pulsed Doppler and >0.55 by tissue Doppler is an indicator of RV dysfunction (Zaidi et al. 2020a). In cardiac surgery, measurements under anesthesia by TEE are significantly lower than those measurements of the preoperative TTE, so RVMPI may be a questionable indicator of global RV function in anesthetized and ventilated patients (Michaux et al. 2010).
7. *Myocardial deformation imaging (RV longitudinal free wall strain)*: It is the change in myocardial shape over time and can occur in three dimensions (longitudinal, circumferential, and radial). RV longitudinal free wall strain is the percentage of systolic shortening of the RV free wall from base to apex. It is measured in the RV-focused four-chamber view by TTE (Rudski et al. 2010) and in the ME four-chamber view by TEE (Vandenheuvel et al. 2019). RV strain in TTE has been shown to correlate with RV EF by magnetic resonance imaging and outcomes (Focardi et al. 2015). A value >−20% by speckle-tracking based myocardial deformation is an indicator of RV dysfunction (Zaidi et al. 2020b). Measurements by TEE and TTE are comparable (Kurt et al. 2012) (Table 2).

In the pediatric cardiac surgery population, RV echocardiographic evaluation is of paramount importance as these measurements correlate with prognosis similarly to the adult population (Kamra and Punn 2019). In general, the echocardiographic views and techniques used have not changed; however, there are some peculiarities:

1. RVFAC has limitations due to the complicated three-dimensional geometrical features of the RV and longitudinal rather than concentric wall motion (Kamra and Punn 2019).
2. TAPSE normal values in the pediatric population are based on their age and BSA, and have already been published (Koestenberger et al. 2014).
3. RVMPI alters with body surface area (BSA), tissue doppler derived RVMPI is approximately 0.37 ± 0.05, whereas pulsed Doppler derived RV MPI is 0.34 ± 0.06 (Roberson and Cui 2007).
4. TAPSV normal values vary based on heart rate, age, and BSA (Roberson et al. 2007).
5. RV longitudinal free wall strain normal range varies in the pediatric population and is available in previous publications (Levy et al. 2014).

Figure 4 illustrates the preoperative echocardiographic images by TEE of a 2-year-old patient diagnosed with Shone syndrome, severe mitral stenosis, subaortic stenosis, and severe PH, who was scheduled for a redo mitral valve repair and LVOT reconstruction. In this case, RV function measurements were altered, which correlates with severe RV systolic dysfunction.

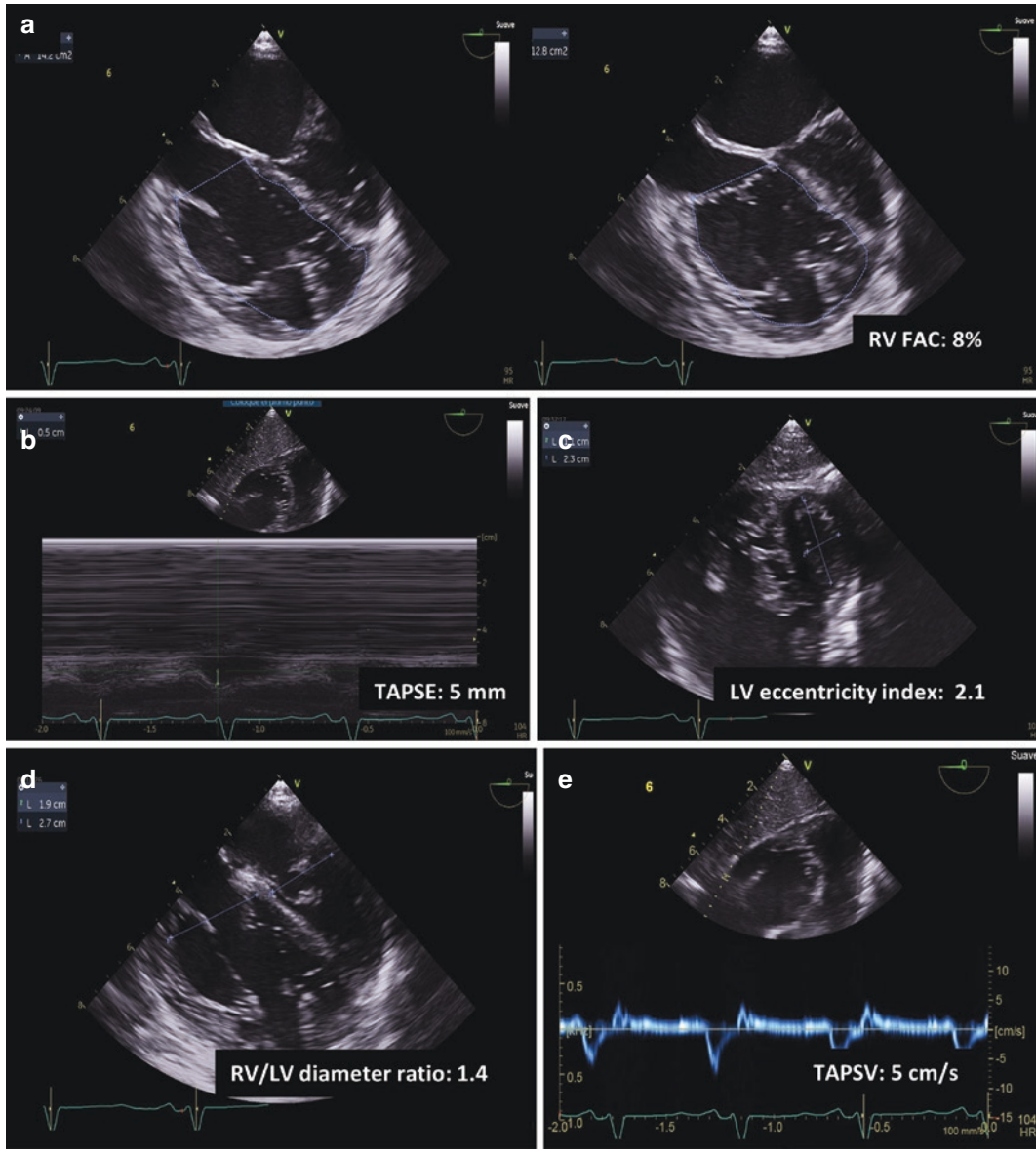

Fig. 4 RV function measurements, all these correlates with severe systolic dysfunction. (**a**) RV fractional area change (FAC) measurement. (**b**) Tricuspid annular plane systolic excursion (TAPSE) measurement. (**c**) LV eccentricity index measurement. (**d**) RV/LV diameter ratio. (**e**) Tricuspid Annular Systolic Velocity by tissular Doppler

Medical Management

How to Protect the RV?

Proper management of oxygenation and ventilation is needed in the prevention and treatment of RV failure since elevations in PVR have profound effects on the RV.

We should identify the patient at risk of RV failure, particularly patients in which an acute increase in the afterload could lead to decompensation. In these patients, a non-pharmacological

approach is proposed as a protective strategy that leads to avoiding factors that increase PVR. The intraoperative management of these patients must be directed to implement all the strategies to prevent acute decompensation; this is accomplished by preventing: hypoxia, hypercapnia, acidosis, hypothermia, and pain and to apply protective mechanical ventilation.

PVR is increased at both ends of the pulmonary volumes. In the poorly ventilated zones, the capillary vessels collapse due to the mechanism of pulmonary hypoxic vasoconstriction. In the zones of high PEEP and tidal volume, the distended alveoli compress the pulmonary vascular bed. The recommended principles of mechanical ventilation for these patients are based on a protective ventilation strategy with a focus on keeping plateau pressure moderated (<27 mmHg), limiting tidal volumes (6 cc/kg) and PEEP (<10 cmH_2O) preferably adapted to the RV function with the guidance of TTE or TEE, avoid hypercapnia with the partial pressure of arterial carbon dioxide ($PaCO_2$) <50 mmHg or ideally less, and maintain normoxia to prevent pulmonary hypoxic vasoconstriction (Klein et al. 1990).

However, these principles could be conflicting because limiting the tidal volume may produce hypercapnia, lowering PEEP may collapse the alveoli, excessive PEEP causes overdistension of the alveoli and all of the above-mentioned situations can cause an increase in PVR that could lead to a dysfunctioning vulnerable RV to fail, which causes decompensation and hemodynamic collapse.

What to Do When the RV Is Failing?

When a patient is already on RV failure the medical management goals should be:

1. Treat the underlying disease.
2. Ventilatory management: besides everything that has been mentioned, we should give a FiO_2 of 100%.
3. Hemodynamic management: includes optimization of all the determinants of the CO (preload optimization, improvement of RV contractility, reduction in RV afterload and increase in RV coronary perfusion pressure).

Preload Optimization

Based on the studies of the physiology of the normal highly compliant RV, the common practice has been to aggressively increase the intravascular volume. However, now is suggested a more conservative approach related to administration of volume in the setting of RV failure (Zochios and Jones 2014; King et al. 2014). The studies support the application of volume only to patients with low CVP because the administration of volume can be deleterious if the preload reserve of the RV is limited. In this stage, more volume expansion results in an increase in the RV EDP, worsening the TR and increasing the septal deviation to the left, and initiating a vicious cycle of ventricular interdependence and ischemia which will lead to biventricular failure (Zochios and Jones 2014; Zarbock et al. 2014; Krishnan and Schmidt 2015; King et al. 2014; Vlahakes 2012).

How to know on which side of the Frank-Starling curve is the patient? The dynamic predictors of the response to fluids, such as variations in pulse pressure, stroke volume, or LV outflow tract velocity-time integral, are based on the effects of ventilation on preload and are reliable when the RV function is normal. However, when beat-to-beat SV also depends on changing RV afterload, as occurs in RV failure, these dynamic indices may falsely signal preload dependency (Krishnan and Schmidt 2015). The respiratory variation of the pulse pressure or the systolic volume is used to predict the response to fluids in patients on mechanical ventilation, the studies show that these parameters are false positives in 34% of the patients with RV failure, leading to the unnecessary administration of IV fluids. Therefore, before administering fluids empirically to patients with known or suspected acute RV failure, echocardiography should be considered for the measurement of baseline parameters to guide the therapeutic management and to evaluate the results. A simple way to predict the results of fluid infusion is a passive leg-raising maneuver with reverse Trendelenburg, and measure objectively the effects of the intervention

with the echocardiographic parameters for RV function (Krishnan and Schmidt 2015).

Unmonitored fluid challenges are inappropriate in the management of RV failure. In patients with volume overload, the reduction in the intravascular volume (through diuresis or ultrafiltration) can improve circulatory function (Price et al. 2010; Zarbock et al. 2014; Itagaki et al. 2012; King et al. 2014).

Improvement in RV Contractility, Reduction in RV Afterload, and Increase in RV Coronary Perfusion Pressure

The principles of the pharmacological management of RV failure are based on the use of different medications with different mechanisms of action to accomplish a decrease in the afterload due to their vasodilatory effect on the pulmonary vascular bed, to improve RV contractility because of their inotropic effect, to guarantee adequate arterial pressure, and to improve the coronary perfusion pressure of the RV (Price et al. 2010; Zarbock et al. 2014; Itagaki et al. 2012; King et al. 2014).

With respect to specific symptomatic therapy, demands a particular emphasis on the fact whether RV dysfunction presents with or without a concomitant increase in PVR. If RV dysfunction presents with increased resistance, therapy primarily requires the application of vasodilators on the pulmonary vascular bed. In the case of normal resistance values, positive inotropic medications are considered the first-line therapy (Zarbock et al. 2014).

There are two classes of positive inotropes: the sympathomimetic inotropes which include Dobutamine, Epinephrine, and Dopamine; and the inodilators which include phosphodiesterase (PDE) inhibitors and Levosimendan.

RV systolic function can be improved with catecholamines that act by increasing intracellular cyclic AMP. Among these, **Dobutamine** exerts inotropic effects via the β1 receptor, and variable vasodilatory effects through β2 receptor stimulation. At doses, up to 10 μg/kg/min improves RV contractility and also vasodilates the pulmonary vascular bed. It may cause hypotension requiring concomitant use of vasopressors, due to β2-mediated systemic vasodilation.

Epinephrine is the resuscitation drug of choice and first-line therapy for CHD surgery with hypotension. It improves BP because it has dose-dependent both α- and β-adrenergic effects. The dose should be carefully titrated since high doses could induce tachycardia, and arrhythmia, increase myocardial oxygen demand, decrease coronary blood flow and increase PVR. In any case, it is an excellent option to augment and maximize RV contractility when used at a low dose for inotropic support (<0.05 μg/kg/min epinephrine infusion) to improve CO without a concomitant rise in PVR (Coleman et al. 2021).

Milrinone, a PDE III inhibitor, is a positive inotrope that also vasodilates both the systemic and pulmonary vasculature. Milrinone increases the global contractility and its effect on LV contractility results in increased RV systolic function through ventricular interdependence. One important issue with Milrinone is its systemic vasodilator effect, and hence, its potential negative effect due to ischemia as a result of diminished coronary perfusion pressure, and can cause significant decreases in both the RV and LV EDP and adversely affect the IVS position worsening the overall hemodynamic stability. Thus, appropriate control of systemic vascular resistance (SVR) must be incorporated into the plan selected for inotropic support. If systemic hypotension develops, a vasopressor must also be given. The combination of Milrinone with Vasopressin may be superior to Milrinone with Norepinephrine in reducing the PVR/SVR ratio (King et al. 2014). The goal is to give inotropic support maintaining the coronary perfusion by having adequate BP.

Levosimendan sensitizes troponin C to calcium in a manner dependent on the calcium concentration, thereby increasing the effects of calcium on cardiac myofilaments during systole and improving myocardial contractility without increasing oxygen consumption. It also enhances myocardial relaxation and diastolic function as a pulmonary and peripheral vasodilator through calcium desensitization, PDE III inhibition, and opening of the ATP-dependent potassium channels. This medication can also induce hypoten-

sion and requires concomitant administration with vasopressors.

The main disadvantage of the intravenous inodilators (Dobutamine, Milrinone, Levosimendan) is that they are not very selective and also that their decrease in the PVR is associated with a decrease of the SVR as well, which decreases BP, putting at risk perfusion to the coronaries and other organs. Furthermore, they can worsen the hypoxemia in the well-perfused but poorly ventilated areas, creating a right to left intrapulmonary shunt. The more specific pulmonary vasodilators can be useful to reduce the RV afterload as well as to manage pulmonary hypoxic vasoconstriction improving hypoxemia.

Inhaled Nitric Oxide (iNO) is a potent gas and rapidly acting selective pulmonary vasodilator that induces relaxation of smooth muscle cells in the pulmonary vasculature by stimulating cyclic GMP release. As a consequence of its short half-life, iON needs to be continuously delivered into the ventilator circuit as an inhalation agent. As it only reaches ventilated regions of the lung dilating those capillaries, results in a better ventilation/perfusion ratio and oxygenation, while it prevents systemic hypotension due to its rapid inactivation by hemoglobin in the pulmonary capillaries. iNO treatment can lead to rebound PH, an increase in intrapulmonary right-to-left shunting, and a decreased oxygen arterial pressure after acute rapid discontinuation. iON is frequently used in post-cardiac surgery patients with RV failure, especially after an orthotropic heart transplant.

PDE 5 inhibitors (sildenafil, tadalafil, and vardenafil) prolong the action of cyclic GMP by inhibiting its degradation by the enzyme PDE 5. Oral Sildenafil has been shown to act synergistically with iNO and to decrease rebound PH after iNO withdrawal.

Prostanoids are found in vascular endothelium and are potent pulmonary vasodilators through activation of cyclic AMP. Currently, commercially available prostanoids are iloprost (intermittent inhaled), epoprostenol (continuous IV), treprostinil (continuous subcutaneous or IV, intermittent inhaled, and oral). Like iNO, inhaled prostanoids improve ventilation/perfusion ratio and do not cause systemic hypotension, but it could happen when administered intravenously.

iNO, oral PDE 5 inhibitors, and Prostanoids result in a synergistic measure for RV afterload reduction through pulmonary vasodilation.

Management with vasopressors is essential because as we have seen in the pathophysiology of RV failure, ischemia is the result of the vicious cycle and perpetrates the downward spiral of the RV function. Likewise, the effects of inodilators on the SVR cause a decrease in arterial pressure and may aggravate arterial hypotension in the patient with hemodynamic instability. Vasopressors can improve coronary artery perfusion and avoid RV myocardial ischemia, also by increasing the SVR and afterload to the LV can help to shift the IVS rightward and improve both LV filling and ejection, improving global CO.

Norepinephrine a vasoconstrictor with a strong α1 and poor β1 effect can effectively be used in patients with acute RV dysfunction and RV failure because it improves RV performance by increasing SVR and CO, the ventricular systolic interaction, and coronary perfusion. As it restores BP there is an increase in cerebral, coronary, and other organs perfusion. In high doses, it can have a deleterious effect by increasing PVR.

Dopamine increases the risk of tachyarrhythmias and is not recommended in cardiogenic shock.

Vasopressin is a non-sympathomimetic vasopressor that acts on the V1 receptor with pulmonary vasodilating properties through a NO-dependent mechanism, according to experimental studies. This attribute is described at low doses and manifests clinically as a reduction in the PVR and the PVR/SVR ratio. It also causes fewer tachyarrhythmias than norepinephrine. However, vasopressin can cause dose-dependent adverse effects on the myocardium, including coronary vasoconstriction (Itagaki et al. 2012; Coleman et al. 2021).

Surgical and Interventional Management of Right Ventricular Failure

In a failing RV patient, oftentimes medical therapy can fail to accomplish adequate stabilization, therefore instituting mechanical circulatory support (MCS) should be considered as early as possible to optimize the outcome and reduce de risk of morbidity and mortality. RV dysfunction is more likely to be reversible compared to LV failure of similar magnitude. Since myocardial recovery is depending on the correct and timely application of MCS, it must unload effectively the RV considering that delaying the MCS is associated with higher morbidity and mortality (Coleman et al. 2021).

Based on the severity the strategy is to use MCS as a bridge to recovery, bridge to transplant (BTT): heart, lung, or combined heart and lung; and in some cases, as destination therapy. To adequately address RV failure, MCS should be implemented based on the pathogenesis of the failing RV: if it is a primary insult of the RV or a result of LV failure or a disease of the pulmonary vasculature (Fig. 5).

1. Temporary implantable or percutaneous RV assist devices (RVAD) and extracorporeal membrane oxygenation (ECMO) are suitable for the primary pathogenesis of the RV.
2. RV failure due to LV or biventricular failure requires temporary or long-term support of the LV and in some cases additionally with RV support. Despite biventricular dysfunction, not all patients benefit from biventricular support.
3. RV failure due to obstructive pulmonary vasculature disease responds positively to ECMO. The physiology resulting from using an RVAD can induce a further increase in the PAPs due to the forward flow, resulting in pulmonary hemorrhage, therefore is not always recommended in this setting.

Mechanical Circulatory Support Device Options

To maximize the success of MCS is imperative to choose the proper device.

Temporary Support

Several percutaneous and surgical devices are available. They can be further classified based on their mechanism of action as "indirect RV bypass" or "direct RV bypass" systems.

ECMO is part of the "indirect RV bypass" category as it does not support the RV directly. However, by decompressing the RV and providing an adequate flow of oxygenated blood to the coronaries, ECMO gives substantial indirect support to the failing RV (Grant et al. 2021).

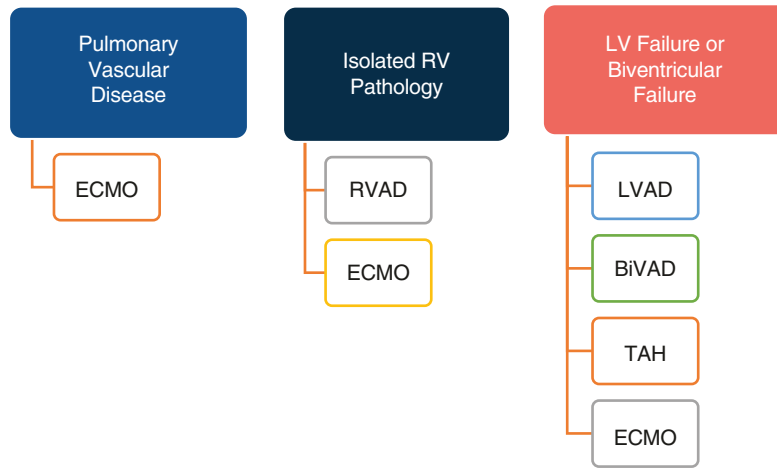

Fig. 5 Mechanical Circulatory Support available based on the pathogenesis of the failing right ventricle. ***RVAD*** (Right Ventricular Assist Device), ***ECMO*** (Extracorporeal Membrane Oxygenation), ***LVAD*** (Left Ventricular Assist Device), ***BiVAD*** (Bi-Ventricular Assist Device), ***TAH*** (Total Artificial Heart)

There are two primary ECMO modalities as well as hybrid forms. Veno-venous ECMO (VV-ECMO) offers respiratory support by withdrawing deoxygenated blood and returning oxygenated blood to the venous system. VV-ECMO relies on the patient's own CO for circulation. Veno-arterial ECMO (VA-ECMO) withdraws blood from the venous system and returns oxygenated blood to the arterial system to provide respiratory and circulatory support.

VV-ECMO is recommended as an initial strategy in patients with RV failure due to purely hypoxemic respiratory failure, even in the setting of shock.

In cases of primary RV failure with intrinsic myocardial injury or RV failure with concomitant LV failure, VA-ECMO is the preferred mode of MCS. VA-ECMO offers several benefits in cases of RV failure, as it can decompress a failing RV, decrease PAP, and restore adequate CO to allow for end-organ perfusion. Multi-organ system failure is the leading cause of death in unsuccessful cases of ECMO initiation, making the timing and strategy selection essential to decrease the risk of irreversible end-organ injury (Grant et al. 2021).

There have been described many other ECMO configurations. VV-ECMO or VA-ECMO can be converted to a hybrid mode in which deoxygenated blood is drained from the venous system, with oxygenated blood returned to both the arterial and venous systems simultaneously, with the exact configuration adapted to the patient's physiology. In Fig. 6, an additional drainage cannula

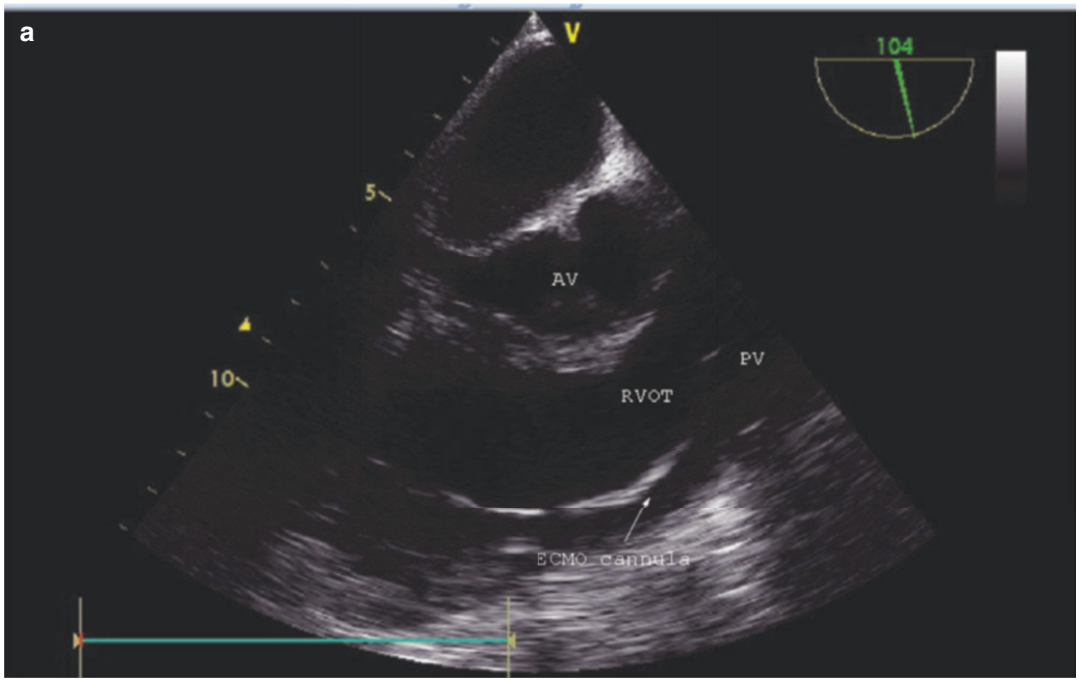

Fig. 6 Transesophageal Echocardiogram (TEE) ME RV inflow-outflow view focused on the outflow showing. (**a**) ECMO Cannula in the RVOT. (**b**) ECMO Cannula advanced into the MPA (Main Pulmonary Artery)

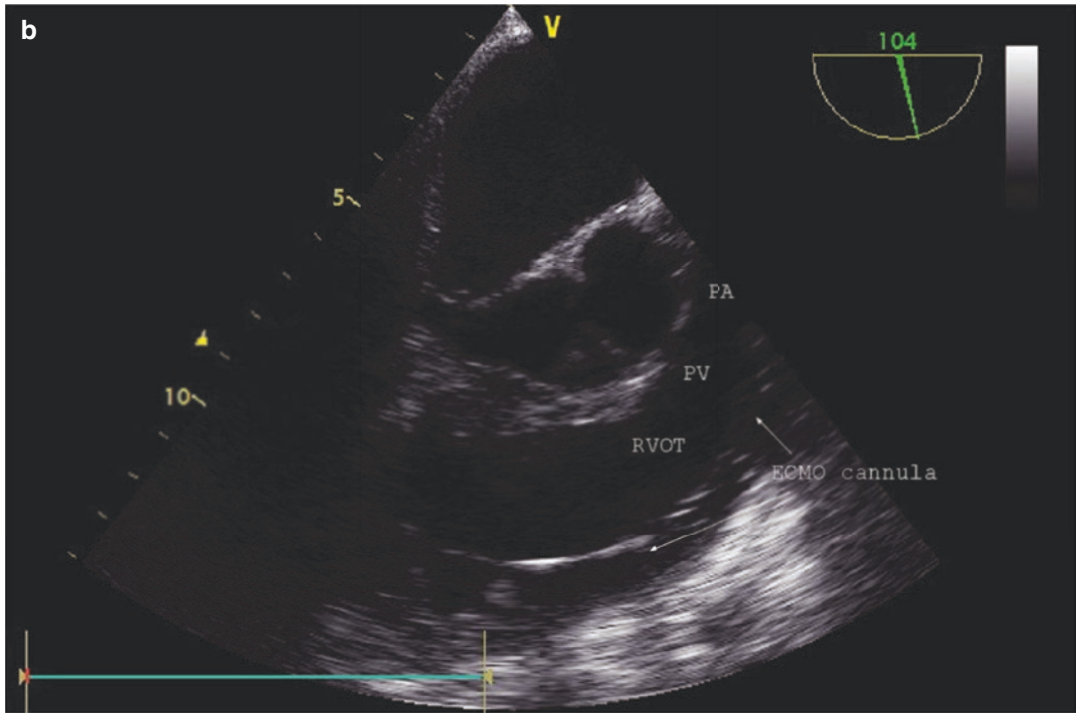

Fig. 6 (continued)

was advanced from the right ventricle outflow tract (RVOT) to the main PA to better unload the RV, configuring a veno-pulmonar-artery ECMO.

For "direct RV bypass," we have the Impella RP (Abiomed Inc., Danvers, MA) a percutaneously implanted micro axial flow RVAD that can deliver a rate up to 4 L/min from the RA into the PA, it is approved to use for 14 days. The TandemHeart® pVADTM (CardiacAssist, Inc.; Pittsburgh, PA) uses an extracorporeal centrifugal flow pump, with two cannulas or a single cannula with a double lumen PROTEK Duo cannula (TandemLife, Inc., Pittsburg, PA) placed percutaneously to deliver blood from the RA to the PA. The CentriMag (Abbott Laboratories, Abbott Park, Illinois) is a short-term surgically implantable device; it requires a median sternotomy or thoracotomy for direct RA and PA cannulation; delivers up to 10 L/min of blood flow, and can provide support for 30 days (Schweiger and Huebler 2018; Arrigo et al. 2019).

Long-Term Support

Most long-term support devices used for RV failure have an off-label use or unapproved indication, as they are designed for LV support. Commonly used devices include the Heartmate 3 (St. Jude Medical, St. Paul, MN) and the Total Artificial Heart (TAH; SynCardia Systems, Tucson, AZ). Patients require close surveillance as they are more prone to complications.

Transplantation

Patients with refractory chronic right ventricular failure (CRVF) are candidates for transplantation once all the possible reversible causes of RV failure have been excluded. A thorough evaluation of comorbidities is crucial to have a positive outcome; this includes chronic kidney disease, cardiac cirrhosis, and protein malnutrition among other contraindications. Also, patients with PH,

right atrial pressure >15 mmHg, and CRVF with a cardiac index <2 L/m/m^2 have a poor prognosis and should be referred for transplantation. In patients with severe PH or CRVF with advanced pulmonary vascular disease, heart-lung or double lung transplantation should be considered. Outcomes of isolated heart and combined heart and lung transplantation have improved in more recent times.

RV Failure in the Pediatric Population with CHD

RV failure is an important determinant of clinical status and outcomes in children with CHD. The RV is at risk for failure from a variety of causes (Friedberg and Reddy 2019; Kendsersky and Ward 2020):

1. Volume overload: There are several congenital lesions that influence cardiac function by overloading the RV with volume as ASD, VSD, TR, repaired tetralogy of Fallot (rTOF) with pulmonary regurgitation, atrialization of the RV (Ebstein's anomaly).
2. Reduced contractility: arrhythmogenic RV cardiomyopathy, post-cardiotomy, increased myocardial fibrosis (ventriculotomy in rTOF and secondary to ischemia), abnormal coronary perfusion, and myocardial ischemia (pulmonary atresia with an intact ventricular septum or coronary anomalies).
3. Pressure overload: RV-PA conduit stenosis after repair of a cyanotic CHD (truncus arteriosus or pulmonary atresia). In the case of patients who have undergone an atrial switch operation for transposition of the great arteries (D-TGA) or a congenitally corrected transposition of the great arteries (L-TGA) where the RV is the systemic ventricle.
4. The coexistence of multiple factors may lead to failure of the systemic RV of the hypoplastic left heart syndrome (HLHS) and in the subsequent stages of palliation (Glenn and Fontan circulation).
5. RV electromechanical dyssynchrony (incoordinate contraction between different RV segments that stems from right bundle branch block) is related to RV dilatation and dysfunction, especially in rTOF patients.

Low CO is observed in approximately 25% of all children undergoing cardiac surgery for CHD and may be related to LV or RV failure. RV failure is more common in the pediatric population than in the adult population and is associated with systemic hypotension and decreased coronary perfusion, which aggravates even further ventricular performance as we have already seen.

Although deviation of the IVS is observed in adults with RV failure, this deviation might not occur in newborns because their myocardium is relatively thicker and less compliant than the adult myocardium.

Indications for the use of inodilators, vasopressors, and pulmonary vasodilators are well described. Milrinone a positive inotropic and vasodilatory agent widely used for patients after surgical repair of CHD has also been investigated in neonates with some data showing an improvement in oxygenation and hemodynamics (Hoffman et al. 2003; McNamara et al. 2006). However, evidence is still very limited in regard to the selection of any specific agent.

MCS in the Pediatric Population with RV Failure

Despite the availability of other modes of support, including ventricular assist devices, ECMO remains the most commonly used form of MCS in the pediatric population. According to the ELSO registry, HLHS was the most common CHD diagnosis for neonates supported with ECMO, and in children, cyanotic CHD with decreased pulmonary flow (e.g., TOF, double outlet right ventricle, and Ebstein's anomaly of the tricuspid valve) were the most common associated with cardiac ECMO (Lorusso et al. 2019).

It is reported that 0.5–6% of children who underwent cardiac surgery for CHD were supported with ECMO (Lorusso et al. 2019).

VA-ECMO is utilized in children with cardiac failure after CHD surgery with post-cardiotomy

shock, in order to augment CO and facilitate respiratory gas exchange. The indications for and rates of ECMO implantation in pediatric patients vary among different studies; however, common indications include failure to wean from cardiopulmonary bypass, cardiac arrest, low CO syndrome, or respiratory failure.

In the study of Klein and colleagues (Klein et al. 1990), RV failure accounted for 14% of the pathophysiology resulting in ECMO support, with biventricular failure, left ventricular failure, and pulmonary hypertensive crisis accounting for 36, 33, and 17%, respectively.

In the pediatric population particularly those children with CHD, it is a challenge to use MCS, especially in the setting of single ventricle physiology. Nonetheless, MCS is used as a BTT considering that 10–20% of all patients with CHD will require a transplant at some point in their lives.

In pediatrics, the most used devices include the Berlin Heart EXCOR (Berlin Heart AG, Berlin, Germany) a pulsatile, para-corporeal pneumatically driven device, used for left ventricular support or biventricular support; one of its major advantages is that it can be used in patients with a body surface area bellow to 1.2 m^2. The Total Artificial Heart (TAH; SynCardia Systems, Tucson, AZ) has also been successfully used in pediatric patients.

Summary

1. RV failure perioperatively and in the ICU is a complication associated with a significant increase in the morbidity and mortality of patients.
2. The knowledge of the complex anatomy and physiology of the RV is necessary to diagnose and manage the syndrome of RV failure.
3. Identifying RV dysfunction at early stages allows an adequate intervention and control of the precipitating events.
4. Echocardiography is not only a diagnostic tool but also allows us to evaluate the impact of the treatment on the RV.
5. The principles of mechanical ventilation for patients with acute RV failure consist of low tidal volumes, keeping plateau pressure moderated and low PEEP with strict avoidance of hypercapnia and acidosis.
6. Volume overload worsens the RV dysfunction. All fluid challenges should be followed closely and monitored.
7. RV has increased sensitivity to changes in afterload. Reduction in RV afterload and optimization of RV preload and contractility form the principles of management. Commonly it requires the combined use of inodilators, vasopressors, and pulmonary vasodilators.
8. It is essential to maintain adequate aortic root pressure to prevent the onset of RV ischemia. Vasopressors are useful in this setting.
9. MCS is essential in the event of failure of medical therapy; using it promptly reduces mobility and mortality. MCS can be used as a bridge to recovery, bridge to transplant, and in some cases as destination therapy.
10. Transplantation becomes a viable option once all the reversible causes of RV failure have been excluded and/or if the severity of it requires referral for transplantation.

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Coronary Artery Anomalies

Pablo Motta, Erin A. Gottlieb,
and Andres Bacigalupo Landa

Abstract

Isolated coronary artery abnormalities (CAA) affect less than 1% of the population. However, the incidence of CAA is up to 11.8–19% of the population in individuals who experience sudden cardiac death (SCD) (Angelini, Circulation 115:1296–305, 2007; Angelini et al., Circulation 105:2449–2454, 2002; Davis et al., J Am Coll Cardiol 37:593–597, 2001; Gentile et al., Circulation 144:983–996, 2021; Oliveira et al., Open J Radiol 4:163–172, 2014). It is the second most common cause of SCD in adolescents and young adults during exertion (Maron et al. 2009). Some CAA only manifest with extreme physical effort when autonomic and endothelial factors cause vasospasm or thrombosis compromising coronary circulation. CAA can present with common cardiac signs and symptoms like ischemia, myocardial infarction, cardiomyopathy, syncope, dyspnea, or SCD. In addition, CAA can present in the context of complex congenital heart disease. Approximately, 7–10% of cases of tetralogy of Fallot and transposition of the great vessels have CAA. Rarely, pediatric patients can develop acquired coronary artery disease. This chapter will also discuss three acquired coronary diseases: Kawasaki (inflammatory), severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) related multisystem inflammatory syndrome in children (MIS-C), and post-transplant coronary artery vasculopathy.

Keywords

Coronary artery anomalies · Abnormal aortic origin of the coronary arteries · Abnormal left coronary artery of the pulmonary artery Kawasaki disease · Multisystem inflammatory syndrome in children Anomalous right coronary artery of the pulmonary artery · Myocardial bridges Coronary allograft vasculopathy

Introduction

Normal coronary arteries originate from the sinuses of Valsalva in the aortic root (Figs. 1 and 2a). The right coronary artery (RCA) takes off from the right coronary sinus, continues through the atrioventricular groove giving branches to the infundibulum anteriorly, and finishes in the inferior inter-ventricular groove.

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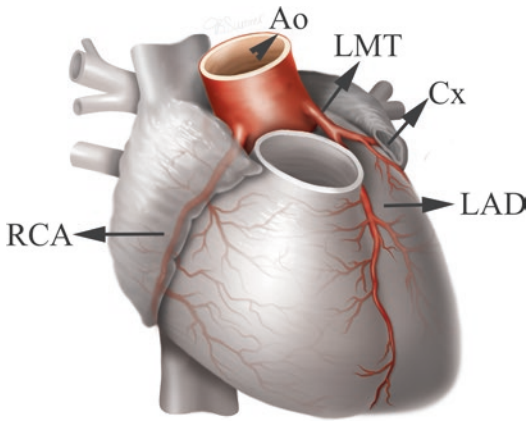

Fig. 1 Illustration of normal coronary anatomy showing the LMT arising from the left coronary sinus and the RCA off the right coronary sinus. The LMT splits after a short segment into the LAD which directs anteriorly and the CX extends to the left atrio-ventricular groove. *LMT* left main trunk, *RCA* right coronary artery, *LAD* left anterior descending and *CX* circumflex. (2014 Texas Children's Hospital (reprinted with permission))

After arising from the sinus of Valsalva, the left main trunk (LMT) divides into the left anterior descending (LAD) and the circumflex (CX) arteries. The LAD artery runs within the inter-ventricular groove to the apex of the heart. The CX extends to the left atrioventricular groove and occasionally (8% of the cases with a left dominant system) gives off the inferior inter-ventricular artery supplying the diaphragmatic aspect of the right ventricle (RV). A balanced system is when the CX and RCA provide a branch each to the inferior inter-ventricular groove (7% of the population). However, occasionally, only the RCA gives off a branch to the inferior inter-ventricular groove (85% of cases with a right dominant system).

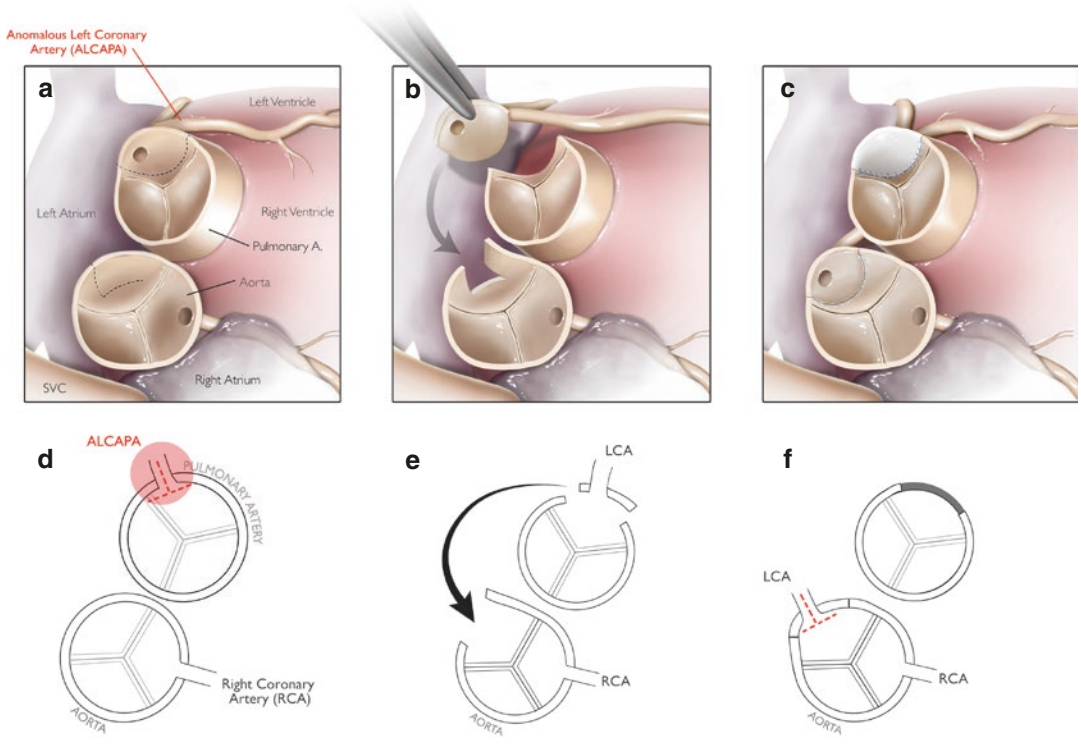

Fig. 2 Illustration showing the ALCAPA (**a**) and (**d**) left coronary artery arising from the left posterior sinus; (**b**, **e**) Harvest of the LCA of the PA; (**c**, **f**) Reimplantation of the LCA to the aorta and patch closure of the PA. *ALCAPA* abnormal left coronary artery of the pulmonary artery, *LCA* left coronary artery. (©2014 Texas Children's Hospital (reprinted with permission))

Embryology

The failure of the development of the coronary sprout is responsible for CAA. In CAA, only one branch develops, causing a single coronary, or both vessels can arise from the same coronary sinus. In addition, the pulmonary endothelial bud may originate from the left coronary artery (LCA), causing an anomalous left coronary artery from the pulmonary artery (ALCAPA).

The low oxygen content increases coronary blood flow mediated by nitric oxide visible in fetal ultrasound. In fetal distress such as hypoxemia, anemia, bradycardia, and intrauterine growth retardation, constriction of the arterial duct may affect the coronary blood flow. Coronary flow evident earlier in fetal life will disappear with those conditions and return once the situations improve.

Classification (Table 1)

The heart is the first functional organ during embryogenesis. After the initial genesis of the ventricular loop, vascular formation follows. The myocardium divides in trabeculations, where vascular beds will form. The subepicardial endothelial plexus eventually connects with endothelial sprouts in the walls of the aortic sinuses. The endothelial nodes form a peritruncal ring, which invades the aortic wall from the outside. Of these sprouts, only two develop a lumen, producing orifices for the left and right coronary arteries. The cardiac function starts at approximately 25 days of gestation. However, coronary artery blood flow is only able to be visualized in the third trimester.

There are several classifications of CAA. The CAA can be classified according to origin, number, course, and ending, with or without hemodynamic compromise. The source of the coronary arteries can be abnormal, such as ALCAPA arising from the PA or in the anomalous aortic origin of a coronary artery (AAOCA) arising from an abnormal site in the aorta (Fig. 2b, c). The AAOCA can present as single or multiple high take-off vessel/s with or without ostial stenosis, originating from the contralateral sinus or the non-coronary sinus. When the left coronary artery arises from the pulmonary artery, the acronym changes to ALCAPA. The coronary artery course can also be abnormal: retro-aortic, inter-arterial, myocardial bridging, and septal. In addition, the coronary distal ending can be unusual and classified as fistulous, arcade, or extracardiac.

The ostial relationship is essential, especially if both coronary arteries arise from the same aor-

Table 1 Classification of congenital coronary anomalies

Anatomic anomaly	Mechanism	Disease
Origin	High take off	Either RCA or LCA
	Single coronary artery	Single LCA or RCA
	Multiple Ostia	RCA & conus branch or LAD & CX different ostium
	Pulmonary origin	ALCAPA
	Contralateral or non-coronary sinus origin	ARCAPA
		ALCA-R
		ARCA-L
		ALAD
Course	Myocardial bridging	LAD (middle segment)
	Duplication	Split LCA origin
		Split RCA origin
Distal ending	Fistula	Fistulas from RCA or LCA to RV, LV, SVC, or PA
	Arcade	RVDCC
	Extracardiac termination	Angiographic communication LAD-RCA
		LCA or LCA to extracardiac vessels (e.g., bronchial vessels, and internal mammary)

RCA right coronary artery, *LCA* left coronary artery, *LAD* left anterior descending artery, *CX* circumflex, *ALCAPA* abnormal left coronary artery off the pulmonary artery, *ARCAPA* abnormal right coronary artery off the pulmonary artery, *ALCA-R* abnormal left coronary artery off right coronary sinus, *ARCA-L* abnormal right coronary artery off left coronary sinus, *ALAD* abnormal left anterior descending artery, *RV* right ventricle, *LV* left ventricle, *SVC* superior vena cava, *PA* pulmonary artery, *RVDCC* right ventricle dependent coronary circulation

tic sinus, to determine a single origin (grade 1) or single coronary artery (grade 4). Finally, it is of critical importance for the clinician to know the hemodynamic consequences of the CAA (Angelini 2007; Angelini et al. 2002; Davis et al. 2001; Gentile et al. 2021; Kim et al. 2006; Molossi et al. 2019; Oliveira et al. 2014).

Pathology

Anomalous Left Coronary Artery from the Pulmonary Artery (ALCAPA)

ALCAPA is the most common cause of myocardial ischemia and infarction in children. In this lesion, the left coronary artery arises from the left posterior sinus of the pulmonary artery (Fig. 3). It is more frequent in males, with a male to female ratio of 2.3:1, and an incidence of 1:300,000. This anomaly is rarely recognized in the neonatal period because the pulmonary pressures and oxygen saturation are similar to systemic pressures and oxygenation. Thus, coronary ischemia does not manifest. After the neonatal period, pulmonary artery pressures decrease progressively, reducing coronary perfusion pressure (CPP) and eventually causing a reversal of flow to the PA ("coronary steal"). The steal phenomenon results in ischemia and decreases left ventricular (LV) function and increases the end-diastolic pressure of the left ventricle. The reduced oxygen content of the blood originating from the PA also aggravates LV ischemia. Unrepaired ALCAPA leads to dilation, infarction, or fibrosis of the LV. Fibrosis can lead to mitral regurgitation. The RCA is usually enlarged, with a typical origin. Collateral circulation is crucial to compensate for this lesion.

Collaterals run over the right ventricular outflow tract (RVOT) or through the interventricular septum and connect the two coronary arteries. The timing of presentation is related to the extent of collateral circulation from the RCA. About 10% of patients with ALCAPA have good collateral flow and do not develop early myocardial ischemia as infants. The clinical presentation may be delayed until adolescence or early adult-

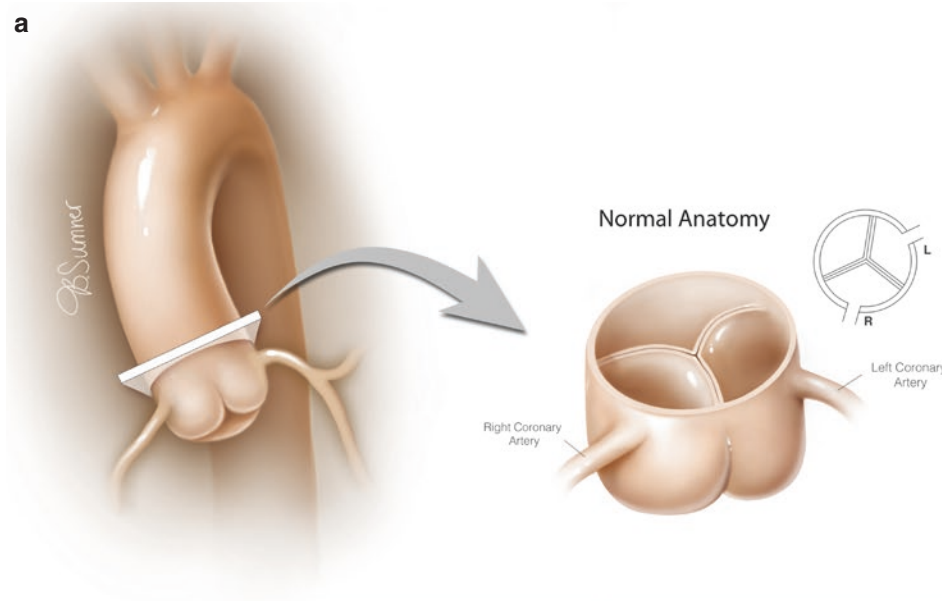

Fig. 3 Illustration showing the AAOCA (**a**) normal coronary anatomy; (**b**) abnormal left coronary from right aortic sinus; (**c**) abnormal left coronary from right aortic sinus with intramural course; (**d**) abnormal right coronary artery from left aortic sinus; (**e**) abnormal right coronary artery from left aortic sinus with intramural course. (©2014 Texas Children's Hospital (reprinted with permission))

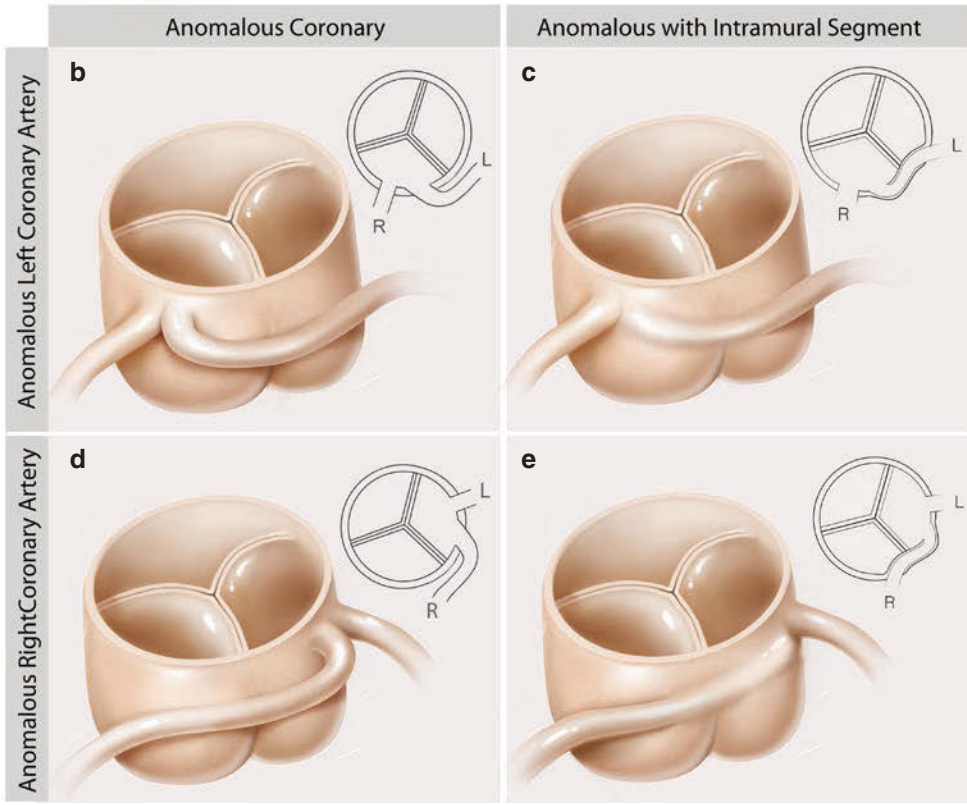

Fig. 3 (continued)

hood. In neonates, symptom may include fussiness, diaphoresis, and failure to thrive. Symptoms range from shortness of breath to chest pain in older children, especially after stress or the Valsalva maneuver. Signs may include heart failure, tachycardia, angina, murmur, and cardiomegaly (Zheng et al. 2011).

Anomalous Right Coronary Artery from the Pulmonary Artery (ARCAPA)

ARCAPA is usually asymptomatic, diagnosed incidentally during cardiac surgery or autopsy. If the patient has a right dominant coronary system with a lack of an intercoronary system, ARCAPA may present as ischemia. It is often associated with other congenital anomalies like tetralogy of Fallot and aortopulmonary window (Vairo et al. 1992)

Anomalous Aortic Origin of a Coronary Artery (AAOCA)

In AAOCA, the abnormal coronary originates from the opposite sinus of Valsalva. AAOCA is usually asymptomatic in infancy, and symptoms develop with exertion in adolescence or adulthood if there is a specific anatomic substrate. Risk factors for developing ischemia include an intramural segment, an interarterial segment (between the aorta and pulmonary trunk), acute angle at takeoff, or ostial stenosis. Early atherosclerosis can also develop in these patients. There are several variants: abnormal left coronary artery from the right aortic sinus (ALCA-R), anomalous right coronary artery from the left aortic sinus (ARCA-L), and abnormal left anterior descending coronary artery from the right aortic sinus (ALAD) (Fig. 2b, c). In the series of AAOCA reported by Davies et al., ALCA-R (58%) was more common than

ARCA-L (36%). The abnormal vessel can take an interarterial, retroaortic, prepulmonic, or septal (subpulmonic) course. AAOCA with an interarterial course, though rare (5%), is most frequently seen in patients with ALCA-R and is associated with the highest risk for sudden cardiac death (SCD) during exercise. The mechanism for SCD involves coronary ostial stenosis or coronary artery compression leading to myocardial ischemia and ventricular tachycardia or ventricular fibrillation. The myocardial oxygen demand increases during exercise, but myocardial oxygen supply is not met. The increased pressure in the cardiac chamber and the great vessels compresses the interarterial segment. Following the Laplace law (Tension = Pressure × Radius), smaller coronary vessels are at the highest risk of compression from the great vessels (Davies et al. 2009; Erez et al. 2006; Shriki et al. 2012).

Stenosis or Atresia of the Left Main Coronary Artery

Stenosis or atresia of the left main coronary artery is due to failure of development or canalization of the left main trunk. However, most of the time, this is compensated for by collateral circulation from branches of the RCA.

Myocardial Bridges (MB)

Myocardial bridges are coronaries that run in the deeper layers of the myocardium and may cause ischemia, infarction, or arrhythmias (Sternheim et al. 2021). Most commonly, MB are seen in the LAD and are at risk for dynamic compression during systole in high catecholamine states affecting diastolic flow.

Coronary Fistulae

Coronary fistulae are abnormal connections between coronary arteries or between coronary arteries and cardiac chambers. These patients are usually asymptomatic (>50%). However, congestive heart failure, cardiac enlargement, arrhythmias, obstruction of veins in the right or left side of the heart, "steal" causing ischemia, angina, infective endocarditis, atherosclerosis, or thrombosis, and embolization may be seen. Patients with pulmonary atresia with an intact ventricular septum often have fistulous communications (30–60%). In patients with associated coronary ostial stenosis, the coronary circulation depends on the RV pressures, and the entity is known as right ventricular-dependent coronary circulation (RVDCC). Patients with RVDCC are at the higher risk for cardiac arrest with induction of anesthesia since CPP is reduced due to decreasing RV pressures (Brown et al. 2006; Powell et al. 2000).

Acquired Coronary Diseases

Inflammatory Diseases

Kawasaki disease (KD) presents in infancy and early childhood. More than 80% of patients are less than 5 years of age. KD usually behaves as a self-limited vasculitis but can affect the coronary arteries leaving long-term damage. Clinical signs typically include skin rashes, conjunctivitis, lymphadenitis, and erythema of palms and soles. There is no specific testing. Treatment focuses on decreasing inflammation with high-dose aspirin and intravenous immunoglobulin therapy during the acute phase. Anticoagulation might be indicated long-term, mainly if there are coronary complications (e.g., coronary aneurysms). Rarely, these patients may require coronary artery bypass grafting (CABG) (Urriola-Martínez and Molina-Méndez 2013).

Coronavirus 2 Related Multisystem Inflammatory Syndrome in Children (MIS-C) and Coronary Disease

In 2019, in Wuhan, China, a novel viral pneumonia presenting acute respiratory distress syndrome was described (Huang et al. 2020). The viral disease was named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and can present as a multisystem inflammatory syndrome in children (MIS-C) with coronary artery involvement (Alsaied et al. 2021). MIS-C is a rare, late

(~4 weeks) complication of SARS-CoV-2. It presents mainly in previously healthy children and is secondary to the severe inflammatory state associated with SARS-CoV-2. The proposed mechanism for myocardial injury caused by SARS-CoV-2 is likely a cytokine storm triggered by an imbalanced response by proinflammatory and regulatory T cells. Fever and fatigue are present in most patients with MIS-C in the context of SARS-CoV-2 infection. The second most common group of symptoms are gastrointestinally related, including abdominal pain, vomiting, or diarrhea. There is a frequent association of MIS-C with cardiac involvement. Therefore, baseline testing should include an echocardiogram, electrocardiogram, cardiac enzyme levels, and a B-type natriuretic peptide level. MIS-C commonly (>50%) presents with shock: vasodilatory, cardiogenic, or both. Coronary artery involvement, though possible, is less common (<25%). Most patients develop small aneurysms during convalescence (z score: 2.5–5). Table 2 compares the differences between KD and MIS-C.

Table 2 Differences between Kawasaki disease and MIS-C

	Kawasaki disease	MIS-C
Demographics		
Age at presentation	Toddler (<8 years)	>8 years
Common ethnicity	Asian	Black and Hispanic
Clinical presentation		
Shock	Rare (5–10%)	Common (50%)
Gastrointestinal symptoms	Rare	Common (>60%)
Laboratory features		
Lymphopenia	Rare	Common
Platelet count	Increased	Decreased
NT-pro-BNP and troponin	Normal or mild increase	Increased
Echocardiography		
Coronary involvement	Common	Rare and minor (<20%)
LV dysfunction	Rare	Common

MIS-C multisystem inflammatory syndrome in children, *NT-pro-BNP* N-terminal pro b-type natriuretic peptide, *LV* left ventricle

Coronary Allograft Vasculopathy (CAV)

Coronary allograft vasculopathy is a multifactorial disease mediated by immunologic, genetic, metabolic, and infectious factors and predisposes the transplanted heart to vasculopathy (Laks and Dipchand 2022; Schumacher et al. 2012). CAV is a progressive, obliterative form of concentric fibromuscular intimal hyperplasia. It is the most common cause of graft failure after heart transplantation in pediatric patients. Younger children and infants have a lower incidence of CAV due to immaturity of the immune system. Due to the denervated state, most patients are asymptomatic, and SCD may be the initial manifestation of this disease. It is graded from grade 0 (not detectable angiographic lesion), grade 1 (LMT <50% occlusion or primary vessel <70% occlusion), grade 2 (LMT <50% occlusion and primary vessel ≥70% occlusion) to grade 3 (LMT ≥50% occlusion or 2 of more primary vessel ≥70% occlusion). Treatment is centered on optimizing immunosuppression. However, in some cases, retransplantation may be necessary (Azeka et al. 2020).

Diagnostic Tests

Electrocardiogram (EKG)

EKG is the initial test for patients with suspected CAA. However, a normal EKG does not rule out the presence of CAA. In ALCAPA, the most common findings are abnormal Q waves with T wave inversion in leads I, aVL, and V4–V6 (**see** Fig. 4). In AAOCA, the EKG is usually normal at rest. In symptomatic patients, the EKG might be abnormal, showing ST and T wave changes in the affected areas during exercise stress testing.

Echocardiography

In ALCAPA, an echocardiogram is helpful in diagnosis by showing the anatomic origin of the ALCAPA and for the assessment of LV function. Pulse and color flow Doppler can help visualize the anomalous origin. A continuous low-velocity

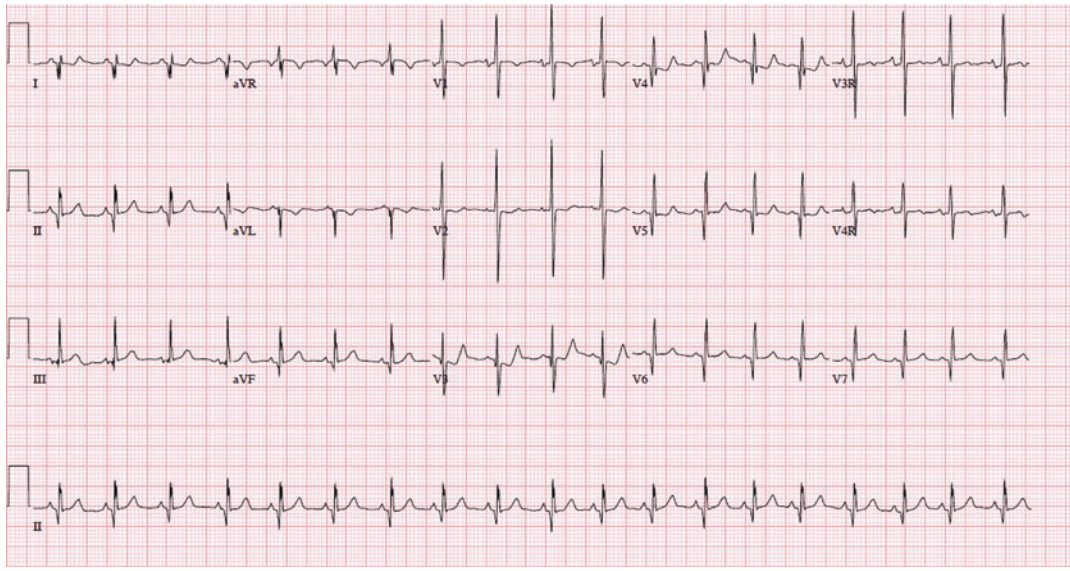

Fig. 4 EKG on an ALCAPA patient showing myocardial ischemia with Q waves and T wave inversion in leads I, aVL, and V4–V6

reverse flow in the posterior wall of the PA with a diastolic prominence is suggestive for ALCAPA. The myocardium may show prominent fibrotic changes like endocardial fibroelastosis. The LV may be dilated with decreased function, particularly at the anterolateral wall. A dilated RCA with abundant septal collaterals may be seen in patients with later presentation due to these compensatory mechanisms. The ratio between the proximal RCA diameter to the aortic root diameter (RCA:AO) is usually >0.20 in ALCAPA, especially in older patients who develop compensatory collateral circulation. The mitral valve needs to be assessed because regurgitation due to papillary muscle ischemia or annular dilatation secondary to LV remodeling may be present (Estévez et al. 2008; Li et al. 2016; Yang et al. 2007) (Fig. 5).

The use of transthoracic echocardiography (TTE) is equivocal in diagnosing AAOCA. TTE does not usually visualize well coronary arteries in older patients. If TTE detects an abnormal coronary artery origin, it may contribute to the diagnosis, but other studies should follow.

Due to the proximity of the esophagus to the aorta, transesophageal echocardiography (TEE) has a better resolution to detect CAA (Kondo et al. 2020). However, TEE is not the first diagnostic tool due to its invasive nature. TEE is useful in the intraoperative period of AAOCA repair (Fig. 6).

Chest Radiography

Infants who present with ALCAPA have abnormal chest radiography. Typical findings include increased cardiothoracic ratio and pulmonary congestion due to LV failure (Fig. 7). On the contrary, AAOCA patients usually have an unremarkable chest radiograph.

Computed Tomography Angiography (CTA)

New generation imaging allows for EKG-gated CTA with three-dimensional post-processing reconstruction. This technique allows visualization of the coronary ostia, coronary morphology, and perfusion during the different stages of the cardiac cycle. Early studies have found a good correlation between CTA find-

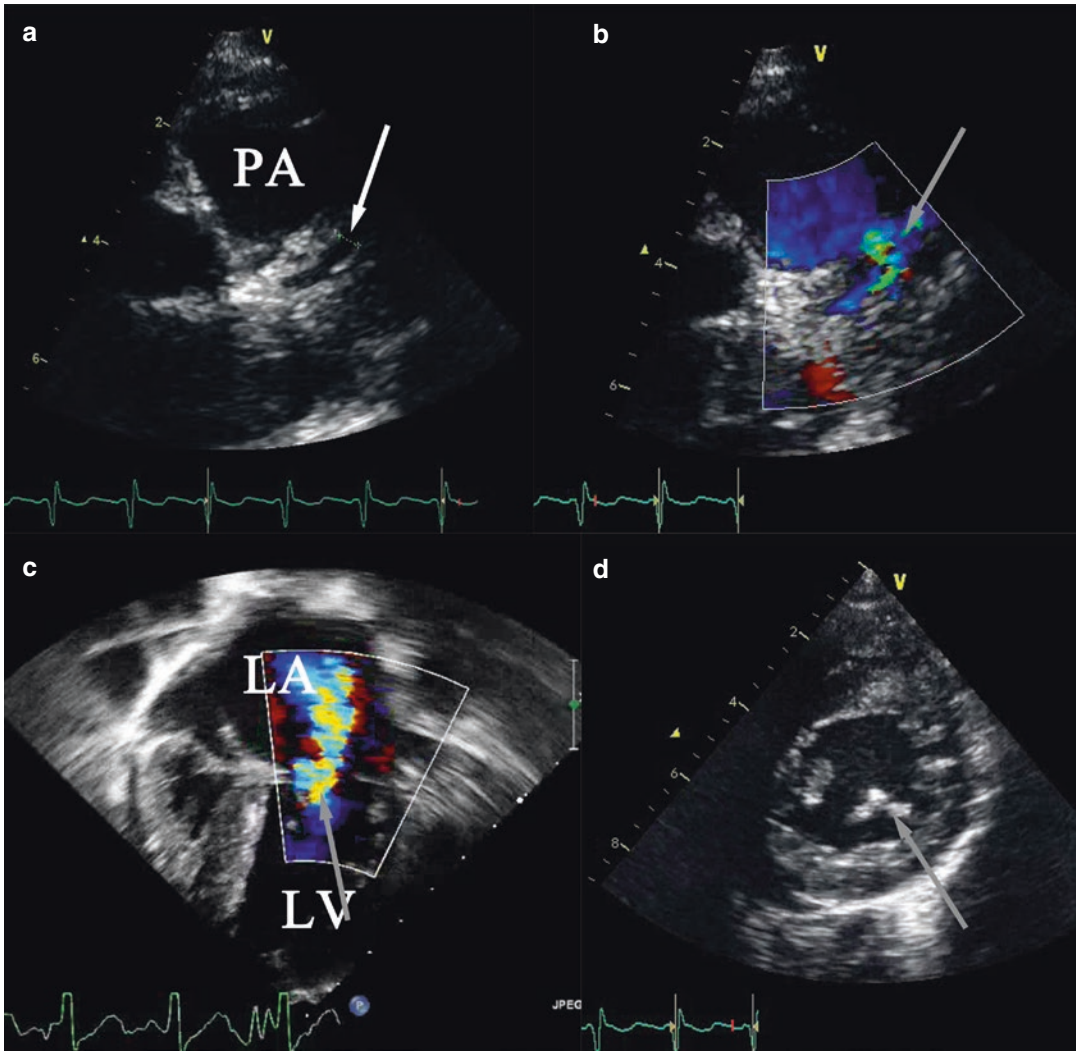

Fig. 5 Transthoracic echocardiography of an ALCAPA patient (**a**) High parasternal view of the pulmonary artery (PA) with white arrow showing the ALCAPA; (**b**) Color flow Doppler from the previous window illustrating retrograde flow from the left coronary to the pulmonary artery (PA); (**c**) Apical four chamber view showing severe mitral regurgitation flow from the left ventricle (LV) to the left atrium (LA) (grey arrow); (**d**) Parasternal short axis view with arrow illustration the calcified posteromedial papillary muscle (grey arrow)

ings and surgical anatomy. With a sensitivity for detection of significant CAA of 80–90%, the main drawback of CTA is the child's exposure to ionizing radiation; however, newer technology decreases radiation exposure (Kim et al. 2006; Pandey et al. 2019; Shriki et al. 2012).

Cardiac Magnetic Resonance Imaging (CMRI)

As a screening tool, CMRI is usually done after a CTA because it is lengthy, and like for most imaging studies, pediatric patients may require sedation. However, the advantage of CMRI is that myocardial function can also be assessed (Fig. 8).

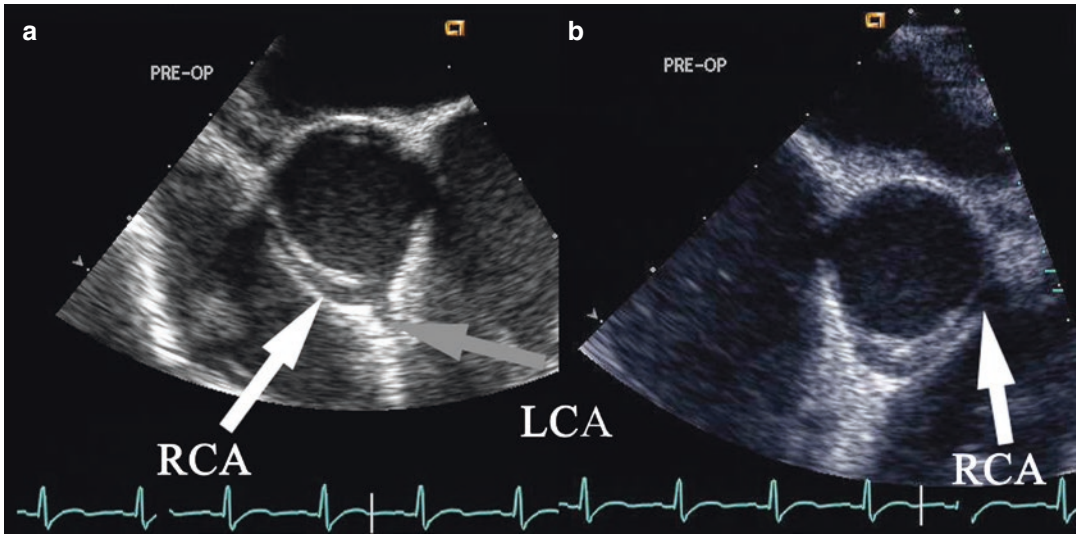

Fig. 6 Transesophageal echocardiography at the mid-esophageal aortic short axis view (**a**) abnormal left coronary artery (LCA) from right aortic sinus (ALCA-R) grey arrow and normal right coronary artery (RCA); (**b**) abnormal right coronary artery from left aortic sinus (ARCA-L) white arrow

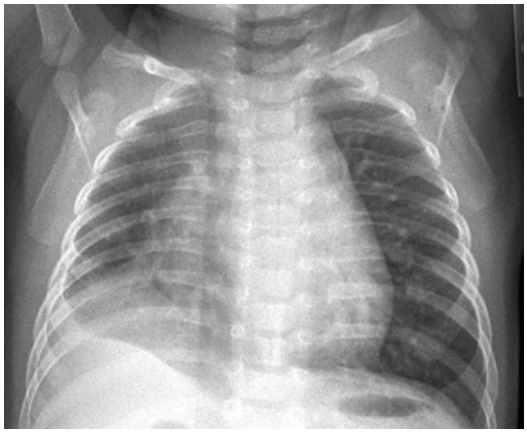

Fig. 7 Chest radiography showing an increased cardiac silhouette and increased pulmonary vascularity

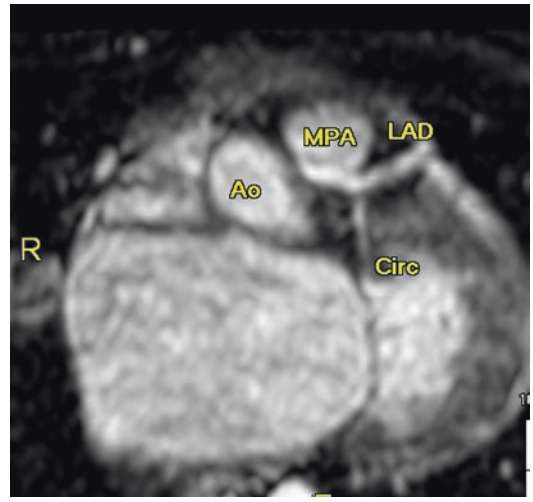

Fig. 8 MRI image showing the origin of the left coronary artery off the main pulmonary artery (MPA) and its bifurcation into the left anterior descending artery (directed anteriorly) and the circumflex (directed posteriorly). *Ao* aorta

Exercise Stress Testing

As previously mentioned, most of the AAOCA patients are asymptomatic at rest. Thus, triggering studies like nuclear perfusion stress (e.g., sestamibi) are necessary to elicit ischemia. Patients who have easily induced ischemia and significant perfusion defects on stress testing are at increased risk for SCD and may require an early surgical approach. Recently, CMRI has taken over nuclear perfusion stress testing due to improved sensitivity accessing function and wall motion. Doan et al described the use of dobutamine and regadenoson for stress CMRI. Dobutamine was safely used to detect inducible hypoperfusion and

abnormal wall motion (AWM) abnormalities in patients with AAOCA (Doan et al. 2021). Regadenoson, an A_{2A} adenosine receptor agonist, produces coronary vasodilation similarly to adenosine but with fewer adverse effects. Doan et al. recently published their experience with regadenoson in children with KD or coronary artery disease (Doan et al. 2019). Aminophylline was administered after stress perfusion sequences to decrease the associated side effects.

Cardiac Catheterization

The gold standard test for coronary artery evaluation is cardiac catheterization. Commonly, it is used as the last resource and only performed in complex cases where echocardiography, CTA, and CMRI tests are inconclusive due to its invasive nature. Two tools can improve the diagnostic capabilities of cardiac catheterization: intravascular ultrasound (IVUS) and measurement of fractional flow reserve (FFR) (Driesen et al. 2018). The 45 MHz IVUS rotational imaging catheter can detect abnormal coronary anatomy including abnormalities of the orifice (e.g., slit-like), compression (e.g., myocardial bridge or intramural course), and atherosclerosis. More than 70% intraluminal narrowing is considered significant. FFR measurement is performed with a pressure wire and calculated as the mean distal coronary pressure ratio to mean aortic pressure. The heart can be stressed by vasodilation (e.g., adenosine) or by increasing myocardial demand (e.g., dobutamine). FFR is considered negative if the ratio is >0.80.

Management Algorithm

During the last several years, a multidisciplinary approach for CAA diagnosis and management at Texas Children's Hospital was developed involving a team of cardiologists, surgeons, and anesthesiologists. The complete algorithm for the management of AAOCA is presented in Fig. 9 (Mery et al. 2014; Molossi et al. 2019).

Surgical Management

The surgical treatment of ALCAPA is direct coronary translocation and patch closure of the PA. Initial reports of LCA ligation have revealed a high mortality rate in infants. Mitral regurgitation usually regresses over time due to improved perfusion. Many of these patients struggle in the initial postoperative period and require inotropic support due to poor left ventricular function. The successful use of left ventricular assist devices (LVAD) has been reported in patients with ALCAPA who have failed to wean from cardiopulmonary bypass (CPB). Reoperation rates are higher in patients who require extracorporeal membrane oxygenation (ECMO) in the preoperative period. The most frequent indication for operation is residual mitral valve regurgitation. Patients who do not recover LV function after coronary reimplantation may become heart transplantation candidates (Cabrera et al. 2015; Imamura et al. 2011). Triglia et al. reported a series of 907 ALCAPA surgical patients (Triglia et al. 2021) with an overall mortality was 6%; mortality was higher in neonates, patients with lower body surface area, and patients who required mechanical circulatory support postoperatively. The simultaneous need for mitral repair did not affect the outcome.

Only AAOCA patients who are at high risk for SCD require surgical repair. The initial repair entailed coronary artery bypass grafting (CABG), but there is the concern of competitive flow from the abnormal coronary impeding maturation of the internal mammary graft. Therefore, CABG is reserved for older patients with concomitant atherosclerotic coronary disease or unusual anatomy that precludes translocation or unroofing. The current techniques used to treat AAOCA include coronary unroofing, coronary translocation, and neo-ostium creation (Figs. 10 and 11). All repairs are performed on CPB with mild hypothermia and aortic cross-clamp through an aortotomy incision (Mainwaring et al. 2014; Poynter et al. 2014).

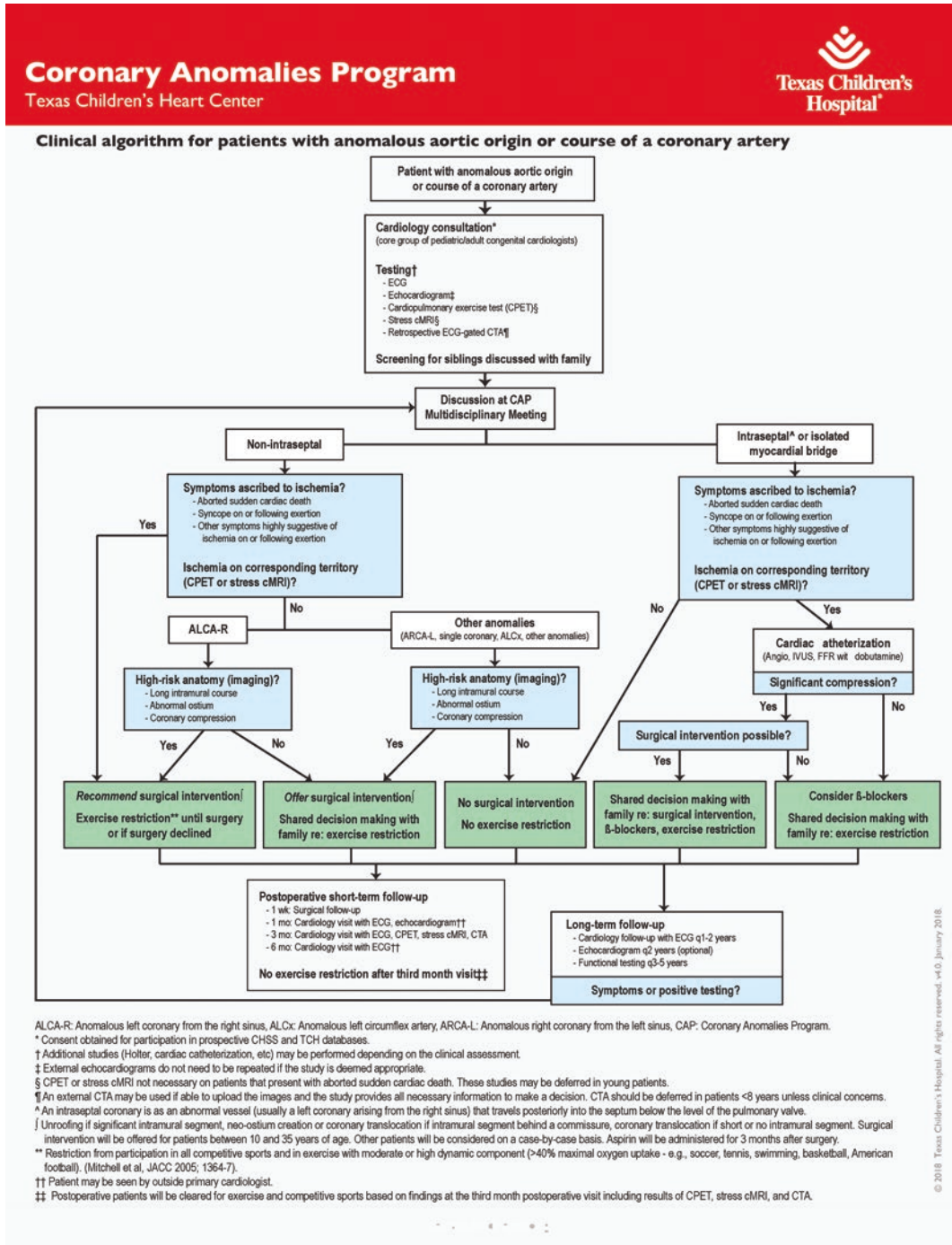

Fig. 9 Clinical algorithm used by the Texas Children's Hospital Coronary Anomalies Program to evaluate and manage patients with AAOCA. (©2013 Texas Children's Hospital (reprinted with permission))

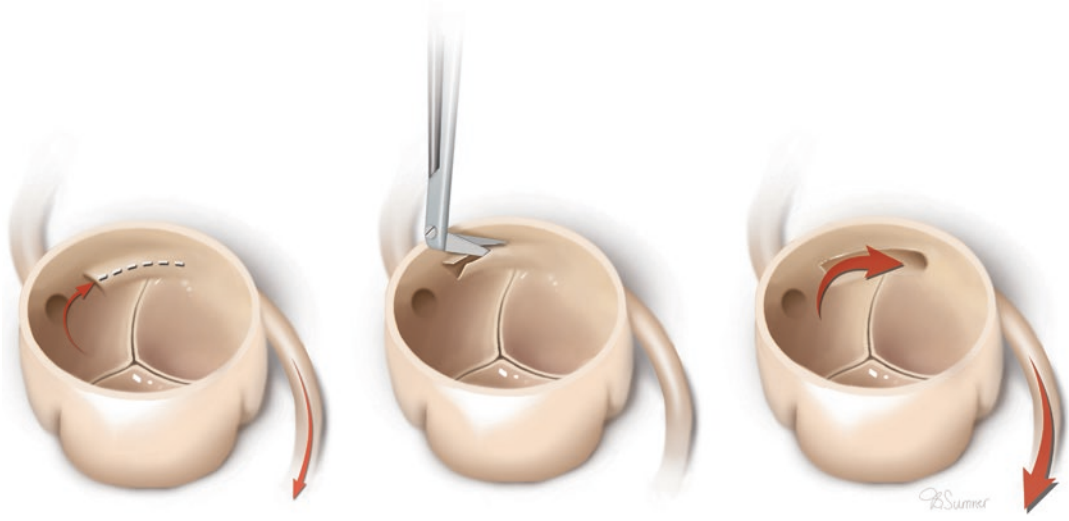

Fig. 10 Technique of coronary unroofing for treatment of AAOCA. (©2014 Texas Children's Hospital (reprinted with permission))

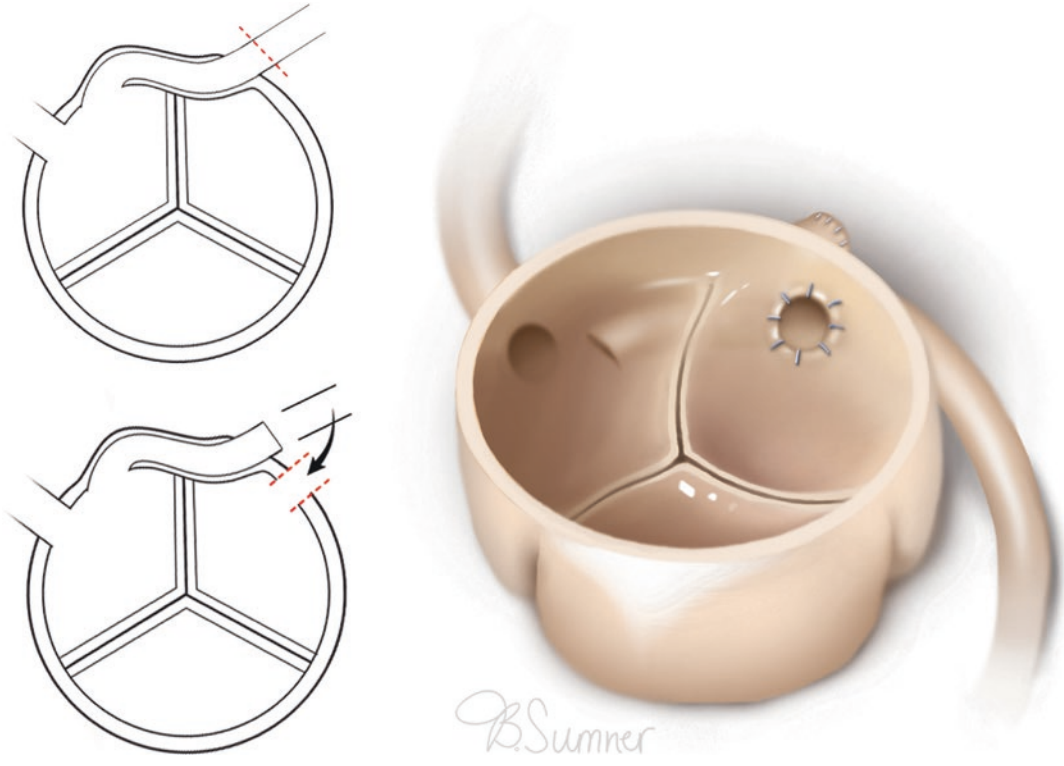

Fig. 11 Technique of coronary translocation for treatment of AAOCA. (©2014 Texas Children's Hospital (reprinted with permission))

Anesthetic Considerations

Anesthesiologists face pediatric patients with CAA in both noninvasive (e.g., CTA and CMRI) and invasive procedures (cardiac catheterization and surgical repair). The coronaries perfuse the cardiac chambers mostly during diastole. The CPP is the aortic diastolic pressure minus the intra-cavitary pressure. Anesthetic management should be tailored to maintain the CPP by increasing myocardial oxygen supply and decreasing myocardial oxygen demand. During induction of anesthesia, it is vital to preserve systemic vascular resistance and avoid tachycardia. Judicious administration of vasopressors and beta-blockers should be considered to achieve such goals (Kloesel et al. 2018).

During stress studies, the anesthesiologist's role is to closely monitor the patient hemodynamics and treat instability and complications if necessary. The most common medications used in stress CMRI are presented in Table 3. Dobutamine is administered through a dedicated intravenous line to avoid catecholamine boluses with fluids or other medication administration. Atropine administration (up to 10 μg/kg) should be considered if the heart rate response to dobutamine is inadequate. One may consider giving atropine earlier rather than later since this may help limit blood pressure overshoot with higher dobutamine doses. In FFR and IVUS, in addition to dobutamine, adenosine (140 μg/kg/min in 3 min) is administered for coronary vasodilatation. The procedure sequence for FFR and IVUS is detailed in Table 4.

Table 3 Cardiac stress MRI medications

	Dobutamine	Regadenoson
Indications	Assess AAOCA	Assess fixed lesions (s/p ASO, Kawasaki's)
	Myocardial bridging	
Dose	10 μg/kg/min infusion	8 μg/kg up to 400 μg as a *bolus* (no infusion)[b]
	Increase by 10 q4 min until desired effect (BP/HR)[a]	
	Max 40 μg/kg/min	
Physiologic effects		
HR	↑↑	↑↑
BP	↑↑	↓
AV block	–	↑
Bronchospasm risk	–	↑/↔
Flushing/HA/GI complaints	++	+

AAOCA anormal aortic origin of the coronary arteries, *ASO* arterial switch operation, *BP* blood pressure, *HR* heart rate, *HA* headache, *GI* gastrointestinal

[a]Atropine may be added (10 μg/kg) if HR response to dobutamine is insufficient

[b]Aminophylline can be used to reverse side-effects

Table 4 FFR and IVUS procedure sequence

Steps	Procedure	Comments
1	Aortogram	
2	Selective coronary injections	
3	Baseline FFR	Significant if <0.8
4	Adenosine administration	
5	FFR repeated	Significant if <0.8
6	Dobutamine stress ± atropine	
7	FFR repeated	Significant if <0.8
8	IVUS evaluation	Significant if intraluminal narrowing >70%

FFR fractional flow reserve, *IVUS* intravascular ultrasound

Symptomatic patients with ALCAPA may have a limited cardiac reserve and significant ischemia. These patients usually require preoperative inotropic support, mechanical ventilation, and even ECMO for stabilization before surgery. During induction of anesthesia in patients with ALCAPA, it is essential to avoid decreases in PA pressure with 100% fraction of inspired oxygen (FiO_2) and hyperventilation because this will aggravate ischemia (due to CA steal). Significant inotropic support may be needed for weaning off CPB. Inotropic agents can improve cardiac function but may also increase heart rate and hence myocardial oxygen demand, worsening ischemia. Nitroglycerin has been successfully used to improve CPP. Cardiovascular depressant effects of volatile anesthetics are often poorly tolerated in infants with ALCAPA, and a high opioid technique may be favored. Most patients are kept intubated and ventilated postoperatively to allow time for ventricular recovery.

TEE is a valuable tool in the perioperative period. The best window to visualize the coronary arteries is the mid-esophageal short-axis view. A pre-CPB TEE is vital to confirm the preoperative diagnosis, examine for AWM abnormalities and estimate the relationship of the defect with the aortic valve. The post-CPB exam is essential to rule out new AWM abnormalities, interrogate the aortic valve, and examine the coronary flow pattern (Fig. 5b).

AAOCA patients rarely develop vasospasm in the postoperative period; hence, nitroglycerin is not routinely used prophylactically. Since the surgical repair involves an aortotomy, blood pressure should be kept within 20% of the baseline to avoid bleeding from the suture lines. The majority of these patients can be fast-tracked and extubated either in the operating room or shortly thereafter in the intensive care unit.

Outcome

More than 90% of undiagnosed or medically treated infants with ALCAPA will die within the first year of life. SCD frequently occurs in untreated older children and adults. Overall, the outcome of surgical repair of ALCAPA is good, even though some patients will need temporary mechanical support. The late mortality of ALCAPA is commonly due to persistent LV dysfunction or arrhythmias.

AAOCA repair is very successful, with minor morbidity and mortality in most reported series (Buratto and Konstantinov 2020). Patients are usually able to return to regular activities without limitations. Mainwaring reported a series of 50 patients with AAOCA followed postoperatively for over 5.7 years, and only one patient required further treatment (transplantation) (Mainwaring et al. 2011). The rest of the population remained symptom-free. In a more recent series, Mery et al. presented 44 AAOCA patients that underwent surgical repair (Mery et al. 2018). Only one patient required reintervention due to an undiagnosed myocardial bridge.

Case-Based Contents

A 2-month-old, 5 kg boy was transferred to our institution for a second opinion regarding new findings of reported depressed heart function. He was well-developed, well-nourished, and in no distress on physical exam. The S1 was regular and S2 was single and prominent. An II/VI systolic murmur at the lower left and right sternal borders was present. The echocardiogram indicated findings consistent with a LV infarct with echogenic papillary muscles, an echogenic left lateral apical myocardium, severely depressed function, and moderate mitral regurgitation. ECG showed Q waves in leads I, AVL, V4, V5, V6, but no acute ST segment changes (Fig. 3). Chest radiography showed an increased cardiac silhouette and pulmonary vascularity (Fig. 7). CMRI under sedation showed a strong clinical suspicion of ALCAPA (Fig. 8). The first troponin level was minimally elevated (0.178 ng/mL). The patient was admitted to the telemetry floor for preoperative monitoring and was started on a low-dose heparin infusion and enalapril. The patient was scheduled for ALCAPA repair on CPB support. The patient underwent repair of the ALCAPA with direct coronary artery reimplantation. However, he could not be weaned off CPB due to poor LV function despite maximal inotropic doses (milrinone and epinephrine). Consequently, he was transitioned to a temporary LVAD (Rotaflow® centrifugal pump). Eventually, the LV function recovered, and the patient was weaned off LVAD on postoperative day three without further complications.

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Fontan and Single Ventricle Patients Undergoing Heart-Liver Transplantation as the Final Palliative Intervention

Leigh Reardon, Tiffany M. Williams, Andrew Disque, Christopher Wray, and Lorraine N. Lubin

Abstract

Single ventricle physiology encompasses a series of rare congenital cardiac abnormalities that are characterized by the absence or hypoplasia of one ventricle. This effectively results in a single ventricular pumping chamber and passive pulmonary blood flow, which has multisystemic consequences as a result of the abnormal hemodynamics and physiology. These abnormalities are rarely compatible with long-term survival if left without surgical palliation in the first few years of life. Surgical treatment of single ventricle physiology has evolved over the past six decades and is characterized by numerous innovations. These include the development of aorticopulmonary shunts, the evolution of partial cavopulmonary connections, and the eventual development of the "Fontan" operation. The Fontan operation has been refined over the years to make it more hemodynamically efficient, but the long-term consequences of the Fontan operation are predominantly related to chronic central venous hypertension and the resulting multi-

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organ consequences, with significant impact on the liver. This chapter explores the increasing experience in patients needing combined heart-liver transplantation (CHLT).

Keywords

Fontan · Single-ventricle physiology · Central venous hypertension · Fontan associated liver disease (FALD) · Plastic bronchitis · Protein losing enteropathy · Veno-Veno ECMO

Physiology and Transplant Outcomes

A "typical" Fontan pressure in an adult is 10–14 mmHg (Ohuchi 2017), which is more than double the normal central venous pressure of an individual with a biventricular circulation. There are inevitable further venous pressure elevations with exercise, or with any conditions that could increase pulmonary arterial resistance. *With only one functional ventricle, flow to the pulmonary arterial bed is* via *passive cavopulmonary connections that are highly dependent on respiratory mechanics and peripheral muscular assistance to maintain adequate cardiac output.* There are other consequences to this passive circulation including hepatic venous hypertension resulting in liver congestion, progressive fibrosis, cirrhosis, and the increased likelihood of hepatocellular carcinoma (Daniels et al. 2017). Chronic mesenteric edema can result in protein loss and malabsorption. Peripheral venous hypertension results in venous stasis and varicosities. By the time of transplantation, many patients have Fontan pressures exceeding 20 mmHg. Furthermore, some patients progress to a physiology known as advanced Fontan-associated liver disease (FALD), whereby cardiac output can be elevated due to a high output and low systemic arterial resistance state encountered with liver failure and decompensated cirrhosis (Munsterman et al. 2019).

Patients with single ventricle physiology represent a special sub-segment of congenital cardiac transplants and are arguably the most challenging patients considered for transplantation. Transplantation in patients with Fontan physiology is often viewed as carrying high or prohibitively high risk given reports of poor survival. As recently as 2009, Lamor et al. reported a 1-year post-transplant survival of 71% in Fontan patients and Davies et al. examined 43 patients with failing Fontan physiology who had a 90-day post-transplant survival of only 65% (Davies et al. 2012; Lamour et al. 2009). Similarly, Tabarsia et al. performed a meta-analysis of 12 retrospective studies from 1995 to 2015 that showed a 1-year post-transplant survival of Fontan patients of 80.3%, and this in a young cohort of in patients aged 7–24 years (Tabarsi et al. 2017).

While the complexity and risk of orthotopic heart transplantation (OHT) and CHLT should not be downplayed, more favorable outcomes in the last 5 years have shifted our understanding of OHT and CHLT in the Fontan patient and is likely due to the following factors: Improved multi-disciplinary patient selection, improved surgical planning and management, pre-transplant optimization, intraoperative congenital cardiac anesthesia care, cardiac intensive care management, and post-transplant care with coordination of care teams.

Shi et al. reported the Australia and New Zealand experience of 34 patients with a median age of 17 (11–31) years having a 1-year survival of 91% (Shi et al. 2016). Additionally, a multi-institutional study published in April 2017 of 38 Pediatric Heart Transplant Study (PHTS) centers from 1993 to 2014 showed better outcomes in a contemporary era analysis. When looking at 402 Fontan patients (<18 years of age) who underwent heart transplant, patients in the early era of transplant (1993–2006) had a 1-year post-transplant survival of 77% and a more contemporary era (2007–2014) had a 1-year post-transplant survival of 89% (Simpson et al. 2017). Better recent post-transplant survival in Fontan patients may reflect process improvements in multi-disciplinary patient selection, surgical planning, pre-transplant optimization, and post-transplant care.

Recently, attention has focused on adults (>18 years of age) as a distinct group of Fontan patients that have faced the adverse consequences of the Fontan circulation for a longer time than their pediatric counterparts. Interestingly, there may be a survival benefit or resiliency to surviving to adulthood with single ventricular physiology and then undergoing OHT or CHLT. Menachem et al. reported a series between 2010 and 2016 at the University of Pennsylvania that included 20 adult congenital heart disease patients of which 8 patients had failing Fontan physiology. The only mortality in their cohort was of a non-Fontan patient (Menachem et al. 2017). Our center, the Ahmanson/UCLA Adult Congenital Heart Disease Center, reported in 2018 a series of 20 adult patients with Fontan palliation—15 of whom underwent OHT and 5 of whom underwent CHLT, with a 100% 1-year survival and single mortality at 3 years post-transplant secondary to severe coronary artery vasculopathy (Reardon et al. 2018). Vaikunth et al. from Stanford also published their experience with en-bloc CHLT in 9 patients with a median age of 20.7 years (range of 14.2–41.3), with a 100% 1-year post-transplant survival (Vaikunth et al. 2019). Each of these centers report success with increasing numbers of patients for CHLT. And there is good multi-institutional evidence that we are underestimating the need for CHLT compared to OHT alone, as patients undergoing CHLT have a significantly improved long term survival.

There is no clear consensus on how to define the failed Fontan. At the Ahmanson/UCLA Adult Congenital Heart Disease Center, *we define failing Fontan physiology in the following way: dysfunction of the Fontan circulation resulting in reduced functional capacity, volume overload, recurrent/persistent arrhythmias, and/or multi-organ dysfunction*. Etiologies may vary and multiple concomitant processes may manifest including ventricular dysfunction, Fontan pathway obstruction, valvular failure, elevated pulmonary vascular resistance, lymphatic insufficiency, advanced liver disease, and persistent arrhythmias.

Evaluation and Listing for Combined Heart Liver Transplantation

Timing for OHT or CHLT in patients with single ventricle physiology is problematic given the variability of presentation. Despite this, early referral to a center with multidisciplinary experience in the management of complex congenital heart disease provides the patient with the best opportunity for a successful outcome rather than being deemed ineligible for transplant secondary to advanced disease.

Applying the typical OHT listing guidelines to Fontan patients may be problematic, but they can serve as a useful reference point—for example, a VO2 max of <14 mL/kg/min is a listing guideline for OHT in those with a biventricular circulation. Indices for exercise tolerance are reduced in most patients with a Fontan with the average well-compensated patient having a VO2 max of around 24 mL/kg/min. In a Fontan patient, one must not only consider the functional limitations of the individual patient but also the multi-organ consequences of failing Fontan physiology.

The decision as to whether a patient may benefit from and OHT versus a CHLT is challenging and fraught with little data to support or refute any given approach. The most commonly encountered scenario in Fontan patients being considered for transplant is the inevitable presence of some degree of liver fibrosis with most patients demonstrating "cirrhotic" changes on imaging, although it has been demonstrated that cirrhosis on biopsy is less common and often does not correlate well with imaging modalities such as CT and ultrasound (Wu et al. 2017). Patients with cirrhosis, regardless of the etiology, may have complicated cardiopulmonary bypass courses and poor outcomes when undergoing cardiac surgical procedures (Wallwork et al. 2019). *The finding of cirrhotic changes on liver biopsy is a strong indication that a combined heart-liver transplantation should be considered. Other clinical/imaging manifestations of cirrhosis and stigmata of liver failure, such as lower esophageal*

varices, ascites, splenomegaly, and thrombocytopenia, are also taken into consideration (Book et al. 2016; Elder et al. 2013; Berg et al. 2017). MELD-XI >17 has been demonstrated to be predictive of worse survival post-transplant in congenital heart disease patients, but in reality it is not a pivotal determinant in our selection process (Berg et al. 2017).

All patients undergoing the transplant evaluation process will have a routine cardiac catheterization, upper endoscopy, and liver biopsy. This is to determine hemodynamics, collateral burden, and addressable conditions such as a Fontan conduit stenosis, assess for varices, and evaluate the degree of liver fibrosis. The endoscopy and liver biopsy are used to better evaluate patients and determine the level of liver dysfunction beyond simple laboratory evaluation, since many patients will have preserved synthetic function while still having significant fibrosis or cirrhosis. *If a patient has biopsy proven cirrhosis (as evidenced by extensive bridging fibrosis), we uniformly recommend a CHLT.* Furthermore, our current practice is that patients with significant bridging fibrosis and stigmata of liver disease with varices and splenomegaly are referred for CHLT. Varices ascites splenomegaly thrombocytopenia (VAST) scores are calculated and presented during our multi-disciplinary meetings (Elder et al. 2013). All patients must have an up-to-date liver biopsy if cirrhosis has not already been demonstrated and CHLT decided upon, preferably within 6 months of listing.

A multi-disciplinary, closely integrated, and frequently communicative team is essential to any program that seeks to perform heart or multi-organ transplantation on failing Fontan patients (Table 1). We have found it extremely helpful to

Table 1 Required services/specialties for Fontan heart and liver transplantation

Team/specialty	Considerations/perspectives
Adult congenital heart disease cardiology	Congenital diagnosis, prior surgeries, anatomy and physiology
Congenital interventional cardiology	Invasive hemodynamic assessment, intervention to address residual venous or arterial stenosis, coil embolization collateral vessels to decrease bleeding during transplant
Congenital electrophysiology	Ablations, arrhythmia and device management
Congenital radiology/ interventional radiology (IR)	Provide detailed anatomic assessments and IR to obtain liver biopsies
Congenital/transplant cardiac surgery	Assess surgical risk and technical feasibility of heart or combined organ transplant
Cardiomyopathy/transplant cardiology	Heart failure optimization, MCS options, management of postoperative immunosuppression and surveillance for rejection
Transplant psychiatry	Screen/treat depression and anxiety
Transplant social worker	Assess social support and compliance
Transplant financial	Assess insurance compatibility and recommend and coordinate necessary changes
Transplant infectious disease	Management and prevention of opportunistic infections
Heart transplant nursing coordination	Primary coordinator of complex evaluation with all team members from point of referral to transplant, patient education
Immunogenetics	Evaluate patient antibody profiles
Pulmonology	Evaluate pulmonary function pre-transplant
Nephrology	Evaluate need for concurrent renal transplant; management of CKD, and perioperative dialysis for volume management
Hematology/oncology	Evaluate chronic leukopenia and thrombocytopenia, rule out occult malignancy.
GI/hepatology	Evaluate whether patient requires concurrent liver transplant, assessment of varices
Liver transplant surgery	Evaluate suitability for concurrent liver transplant
Liver transplant nursing coordination	Coordinate liver evaluation, patient education.
Cardiac and liver transplant anesthesiology	Preoperative anesthesia evaluation, identifying modifiable risks and making detailed plan for perioperative anesthesia plan
Blood Bank	Prepare for massive transfusions

have meetings on a regular basis (typically ever 2–3 weeks) with the cardiac congenital/transplant surgical/medical teams, hepatology and liver transplant surgical teams, the adult with congenital heart disease (ACHD) team, and renal/pulmonary and other medical consultants to discuss these patients in depth and review their imaging studies together. Reviewing a patient for OHT and CHLT in an initial core stakeholders meeting can take upwards of an hour or more per patient. We have found it vital to have a small group of dedicated team members familiar with the intricacies of a Fontan transplant spend time reviewing each patient and using each patient as a programmatic continual learning exercise.

Important considerations in addition to Fontan and hepatic function to consider include:

- *Multiple prior operations can result in restrictive lung disease due to impaired diaphragmatic function and fibrosis.* Diaphragmatic function may range from mild decrease in diaphragmatic excursion to complete hemidiaphragm paralysis due to phrenic nerve injury. Nonetheless, plication at the time of transplant for patients with borderline restrictive lung disease may be considered.
- Diaphragmatic atrophy, as a part of skeletal muscle mass loss, is associated with chronic liver disease and may contribute to failing Fontan patient symptoms and contribute to difficulties in weaning mechanical ventilator support in the postoperative stetting.
- Rarely, patients with protein losing enteropathy may also have a *plastic bronchitis* which carries significant perioperative implications for oxygenation and separation from cardiopulmonary bypass after OHT or CHLT; therefore, plastic bronchitis should be ruled out with chest imaging prior to listing. The use of perioperative veno-venous ECMO may be used to bridge these patients perioperatively as needed.
- Nephrology evaluation is indicated in this population due to chronic low cardiac output and renal venous congestion. Baseline chronic kidney disease (CKD) is generally present in this patient population due to chronic heart failure, passive congestion, renal toxic medications, and contrast exposure. Post-transplant, renal function often improves in patients with stage I-II CKD due to improvement in cardiac output; however, continuous renal replacement therapy (CRRT) is often needed in the immediate post-transplant period for optimization of fluid status.
- The baseline coagulation status of these patients should be delineated preoperatively and the post-surgical coagulopathy which is multifactorial and often profound.

A separate focused, surgical meeting after acceptance in the full heart and/or liver committees to discuss the surgical/operative and perioperative plan is necessary for those with complex anatomy and those requiring multi-organ transplantation. At our institution, this meeting includes the cardiac and liver transplant surgical teams, cardiac and liver anesthesia teams, as well as the perfusionists and specifically addresses the technical steps involved in coordinating and orchestrating such a complex surgical undertaking.

Perioperative Optimization

Once listed for CHLT, patient optimization we believe plays a major role in successful outcomes. While awaiting transplant, ACHD patients with tenuous hemodynamic status or evidence of progressive end-organ damage may benefit from inpatient admission and listing, as this provides an opportunity for ongoing optimization prior to transplant.

The degree of intraoperative and postoperative bleeding is the single most important cause of intra- and perioperative mortality. The difficult to control operative bleeding is commonly due to the presence of aortopulmonary (AP collaterals) and to a lesser extent venovenous (VV) collaterals. A strategy for targeted transcatheter coil embolization or device occlusion of VV and AP collaterals prior to transplantation should be considered to mitigate surgical risk. (Fig. 1) Bleeding particularly on chest entry increases

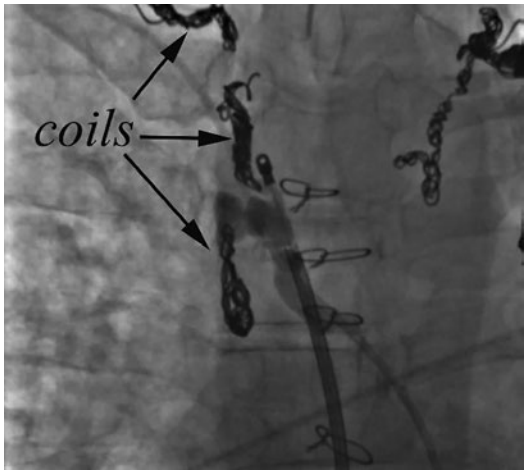

Fig. 1 Transcatheter coiling of AP collaterals preformed to reduce surgical bleeding during CHLT

the complexity of the procedure, potentially increases donor organ ischemic times, and may necessitate significantly larger blood product transfusions during the transplant—thereby increasing the inflammatory response, further burdening the renal system, and potentially sensitizing the patient to alloantibodies. It is our practice to schedule coil embolization catheterizations after the patient has been accepted for transplant and not to list until the majority of the AP and VV collaterals have been occluded. Most of our patients require more than one visit to the catheterization laboratory given the high burden of collaterals encountered and the importance of avoiding large iodinated contrast loads and excessive procedural radiation. Patients who are listed but have not received an organ will have repeat surveillance catheterization to assess for recurrent collateral burden every 3 months or as deemed necessary by clinical evaluation.

Continuous infusion of inotropes can improve organ perfusion, and careful titration of diuretics can maintain the patient in a euvolemic state, thus mitigating risk at the time of transplant and possibly even reverse some of the end organ damage caused by venous congestion and low cardiac output. We closely monitor daily weights and Fontan pressure via a PICC line in order to closely titrate medical therapies. Effective preoperative optimization improves hemodynamic stability during induction of general anesthesia and in pre-cardiopulmonary bypass (CPB) period. This shortens CPB duration and reduces blood loss by allowing surgical teams to carefully dissect heart out without injuring diaphragm, mediastinal structures and obtain hemostasis before heparinization for CPB.

All our OHT and CHLT patients are operated on by experienced congenital heart disease/heart transplant and liver transplant surgeons and patients are made status 7 if there are team members who are unavailable.

Intraoperative Considerations

Liver Transplantation Considerations

Liver transplant (LT) patients present with myriad signs and symptoms of end-stage liver disease (ESLD). Cirrhosis impacts all major organ systems. Neurologic implications include hepatic encephalopathy and reduced levels of consciousness. Gastrointestinal sequellae include esophageal variceal hemorrhage, ascites, and spontaneous bacterial peritonitis. Pulmonary manifestations include hepatic hydrothorax, hepatopulmonary syndrome, porto-pulmonary hypertension, and atelectasis due to tense ascites. The cardiovascular effects of cirrhosis are manifested in a syndrome known as cirrhotic cardiomyopathy and include a hyperdynamic circulation with decreased systemic vascular resistance (SVR), vasoplegia, and autonomic dysfunction. ESLD produces a balanced coagulopathy that may lead to hypocoagulable or hypercoagulable states depending on the clinical scenario. Decreased hepatic synthesis of coagulation factors, splenic platelet sequestration, dysfibrinogenemia, and pancytopenia contribute to this complex coagulopathy. The renal system is impacted by the development of hepatorenal syndrome, a form of functional renal failure that may be reversible with improved hepatic function such as after LT. Electrolyte and acid-base abnormalities are common and include hyponatremia, hyperkalemia, and metabolic acidosis. The anesthetic management of surgical patients with ESLD is therefore very challenging. The pathol-

ogy of end-stage heart failure and liver failure in the setting of congenital heart disease anatomy makes the management of combined OHT/OLT one of the most challenging cases that cardiothoracic and liver transplant anesthesia teams may encounter (Fig. 2).

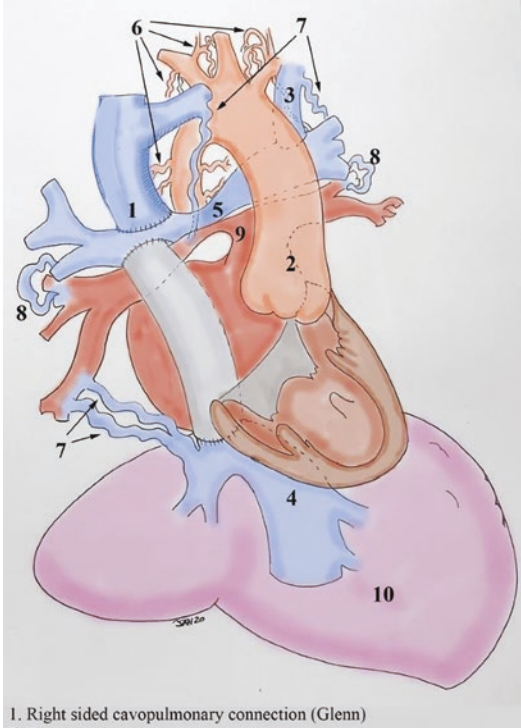

Fig. 2 Anatomic and surgical considerations when considering heart or heart and liver transplantation in a patient with heterotaxy, transposition, total anomalous pulmonary venous connection (previously repaired), intra-atrial tunnel Fontan, left sided superior vena cava, numerous arterial and venous collaterals, bilateral Glenn shunts and pulmonary artery stenosis/hypoplasia. Every one of these factors requires special consideration and appropriate planning to ensure success. In selected complex cases using 3D printed models allows for advanced surgical planning and optimal repair of vascular anomalies. (From*: Orthotopic Heart and Combined Heart Liver Transplantation: the Ultimate Treatment Option for Failing Fontan Physiology, Permissions Springer Life Sciences and Reardon et al.*)

Phases of Liver Transplantation

LT surgery is classically divided into three individual phases, known as the preanhepatic, anhepatic, and neohepatic phases. The preanhepatic phase includes the surgical dissection, mobilization, and eventual removal of the native liver. In addition, all relevant vascular structures are prepared for surgical anastomoses. These include the suprahepatic inferior vena cava (IVC), infrahepatic IVC, portal vein, and hepatic artery. The preanhepatic phase has the potential for massive hemorrhage, hemodynamic instability, coagulopathy, hyperkalemia, metabolic acidosis, and the need for massive transfusion. The management of this phase may be very challenging and often requires administration of high-dose vasopressors, interventions to manage acid-base and electrolyte disorders, and targeted treatment of complex coagulopathies. In select cases, intraoperative dialysis and veno-venous bypass may be employed.

The anhepatic phase begins with removal of the native liver. Cross-clamping of the IVC, portal vein, and hepatic artery is required for the hepatectomy. Cardiac preload is significantly reduced when the IVC is clamped using a bicaval surgical technique. A piggyback surgical technique may allow for partial IVC clamping, resulting in partial IVC venous return to the heart. In addition to a reduction in preload, the exclusion of the liver from the systemic circulation results in a complete loss of any residual hepatic function. Acidosis, hypothermia, coagulopathy, fibrinolysis, oliguria, and vasodilatory shock often worsen during this phase. Portal vein thrombectomy may be required in patients with known portal vein thrombus, complicating the surgical procedure. During the anhepatic phase the vascular connections between the recipient vessels and the donor IVC and portal vein are completed.

Reperfusion of the donor liver is the critical event that marks the beginning of the neohepatic phase. Significant, yet transient disturbances may include hyperkalemia, metabolic acidosis, hypothermia, and hypocalcemia. Additionally, post-reperfusion syndrome (PRS) occurs in 30–50% of LTs and presents with acutely reduced SVR

and increased PVR immediately following reperfusion (Chui, Jeong) (Jeong 2015). PRS is associated with prolonged cold ischemia times and with sub-optimal donor grafts (Chui, Jeong) (Jeong 2015). Preemptive treatment prior to reperfusion with intravenous calcium chloride, vasopressors, epinephrine, and sodium bicarbonate is widely employed by LT anesthesiologists. After reperfusion the arterial anastomosis is completed, resulting in complete organ perfusion. Signs of graft function or dysfunction may become apparent during the neohepatic phase. A reassuring liver graft will demonstrate increasing pH, rising plasma calcium levels, increasing temperature, bile production, increasing urine output, and reduced vasopressor requirements. Early allograft dysfunction may present with worsening of metabolic acidosis, hypothermia, or coagulopathy. After the arterial anastomosis is completed in a single organ transplant, the major surgical bleeding is addressed, the bile duct is connected, the abdomen is closed, and the patient is transitioned to the ICU.

Anesthetic Considerations for Combined Liver Transplant and Heart Transplant (OLT/OHT)

The phases of LT and the surgical approach are similar for LT in the setting of combined OLT/OHT. However, the pathophysiology inherent during LT may be poorly tolerated by the newly transplanted heart. Physiologic derangements that occur routinely during LT such as large preload changes associated with caval clamping and unclamping, large vasopressor dosing, metabolic acidosis, hypothermia, acute vasoplegia associated with reperfusion, and other unpredictable events may have adverse effects on the newly reperfused cardiac graft. . Because of the complexity of these cases, there is no standard surgical and anesthetic approach for the management of these cases. Each case must be individualized to the specific patient and to the institution. A multi-disciplinary approach must be utilized to determine the best plan for the specific case at hand. Some patients with congenital cardiac deformities may have altered atrial situs or abdominal vessel deformities which may necessitate en-bloc heart-liver organ procurement and graft implantation, as opposed to the usual transplantation sequence. Reconstruction of anastomotic sites is frequently required and is part of the surgical plan.

In addition to the usual steps of LT, some portions of the procedure may be delayed and addressed at another time. Surgical bleeding may be significant due to multiple previous cardiac surgical procedures, collateral burden, complex coagulopathies associated with cardiopulmonary bypass in the setting of prolonged surgery and underlying liver disease. The biliary connection is typically deferred for a later surgical procedure and following adequate hemostasis the abdomen is packed and temporary closure is performed. Following induction, combined OLT/OHT patients should be appropriately prepared to undergo both procedures. An arterial line and large-bore multi-lumen central venous access are necessary. Given the possibility of central venous vessel occlusion or congenital anatomic variations, patent upper venous anatomy should be assured by preoperative venous imaging and specifically reviewed during the multi-disciplinary team meeting. A pulmonary artery catheter is placed at the same time as CVC access is established, but the PAC must be withdrawn to the SVC position prior to heart transplantation, such that it does not interfere with venous cannulation for the heart transplant. Transesophageal echocardiography is standard for the care of cardiac transplantation and is utilized during the combined OHT/OLT procedure to analyze cardiac anatomy. Preload and function.

Mechanical Circulatory Support Options for Liver Transplantation

There are two major options for mechanical circulatory support (MCS) for the liver transplantation portion of the procedure: veno-venous bypass and cardio-pulmonary bypass. Each type has distinct advantages and disadvantages.

Veno-venous bypass (VVB) is a method of hemodynamic support where venous blood is diverted from one area of the body and returned to another venous connection. Specifically for LT, VVB is utilized to divert blood from the IVC and mesenteric circulation to an area above the IVC cross-clamp, such that the patient's heart receives a higher fraction of preload. VVB may be performed during LT when hemodynamic instability occurs during the anhepatic phase that is refractory to routine vasopressor administration and volume resuscitation. VVB may also be employed to provide for decompression of the portal circulation to improve surgical conditions during the dissection phase. VVB does not require systemic heparinization and is routinely performed at some LT centers. The setup for VVB includes an ECMO circuit and three cannulas. The inflow cannulas to the ECMO system for VVB are placed in the femoral vein, which is accessed via a surgical cutdown, and in the portal vein. These two cannulas are joined together and blood is delivered to the pump. The outflow cannula from the VVB system is typically sent to the left axillary vein, which is also accessed via surgical cutdown. A significant disadvantage of VVB for patients with a history of heart failure is related to the outflow cannula placement. Many heart transplant recipients have intracardiac defibrillator (ICD) systems placed near the axillary vein locations for the outflow cannulas, which would contraindicate placement. In the case of combined heart/liver transplantation cases, the outflow cannula may be placed directly in the right atrium.

Cardiopulmonary bypass (CPB) is required for the heart transplant. In some centers, CPB is continued after completion of the heart transplant and maintained throughout the LT. When CPB is used for the LT, there are important considerations. The systemic heparinization required for CPB permits the use of cardiotomy suction to drain surgical bleeding during the LT procedure directly to the pump reservoir. Given the likelihood for significant hemorrhage associated with the dissection phase, using cardiotomy drainage to the pump can significantly reduce blood product administration. The excessive use of standard surgical suction during bleeding may result in significant intravascular volume loss. Likewise, the use of cell salvage instead of cardiotomy drainage results in more red blood cell loss and dilution of clotting factors. For LT performed on CPB, it is logistically much easier to deliver blood products directly to the CPB reservoir than by venous administration.

A major advantage to continuing CPB for the LT is that hemodynamic stability is much easier to maintain during the critical events of LT periods. Particularly, IVC clamping and unclamping, venting of caval and portal vascular connections, portal vein thrombectomy, graft reperfusion, and the arterial anastomosis are facilitated with the use of CPB. Most importantly, continuation of CPB protects the new cardiac graft from major hemodynamic and metabolic insults that may be poorly tolerated otherwise. The most critical reason for doing the liver transplant portion of the operation is the maintenance of hemodynamic stability during CPB which will decrease major shifts in preload, afterload, acidosis, and temperature. The disadvantages of continuing CPB for the LT must be considered by the surgical and anesthesia teams as well. The prolonged CPB duration may result in severe vasoplegia, renal dysfunction, complex coagulopathy, and neurologic complications. Institutions must develop flexible perioperative plans that are individualized for each patient and the associated clinical conditions.

Intraoperative and Perioperative Hemodialysis

In some transplant centers, intraoperative continuous renal replacement therapy (CRRT) may be used during LT in patients with underlying advanced renal dysfunction. In patients with renal failure, CRRT may be invaluable for maintaining electrolyte and acid-base stability during the procedure. The CRRT system can be run via a dedicated percutaneous or tunneled dialysis catheter. Alternatively, it may be inserted into a CPB or VVB system. An advantage of using CRRT through a dedicated dialysis catheter is that it can be available for the duration of the

entire procedure, if needed. CRRT is associated with potential complications such as embolic events, line thrombosis, and hypothermia. When CRRT is performed on CPB it allows for easier maintenance of normothermia secondary to the effect of the heat exchanger associated with the CPB circuit. The downside of this approach is that the CRRT must be discontinued whenever the bypass is stopped.

The Management of Intraoperative Vasoplegia and Massive Transfusion for Combined OHT/OLT

The two critical perioperative challenges that characterize the CHLT procedure are profound vasoplegia and severe hemorrhagic coagulopathy. The vasoplegia and coagulopathy are both likely multifactorial and our approach to both of these problems is continuously evolving as we strive to protocolize care and optimize outcomes. Our current approach to vasoplegia includes the use of vasopressin and norepinephrine infusions with usage of methylene blue, hydroxocobalamin, and/or angiotensin II in refractory cases. Angiotensin II is titratable as opposed to methylene blue which can be unpredictable in its action and is contraindicated in G6PD deficiency, renal insufficiency, and in patients using SSRI medications.

Severe hemorrhage due to surgical bleeding, collaterals, and coagulopathy are notable in most patients undergoing CHLT. The surgical bleeding is best controlled by ensuring adequate hemostasis during surgical dissection and utilizing peripheral cannulation if sternotomy is deemed to be high risk given the retrosternal proximity of vascular or cardiac structures. It is best to control potential bleeding from AP and VV collaterals preoperatively with extensive coiling. The multifactorial coagulopathy is frequently due to prolonged cardiopulmonary bypass, the inflammatory response, liver dysfunction, and consumption of factors and platelets. All patients receive anti-fibrinolytic agents such as aminocaproic acid throughout the case. The use of a rapid infusion device and transfusion of multiple blood products is standard in these cases. Serial ROTEM (Rotational Thromboelastometry) assessment of coagulation enables guidance of transfusion products. A prolonged period to obtain hemostasis is generally required after separation from bypass. The use of desmopressin or recombinant factors such as Factor VIIa and prothrombin complex concentrate (Kcentra or Profilnine) are frequently required for hemostasis. Recombinant factors must be used judiciously due to the risk of thrombosis particularly of the hepatic artery. When intractable vasoplegia, severe coagulopathy, and high inotropic support are present, a decision for early mechanical circulatory support (MCS) may need to be made as a rescue therapy. In many cases, these patients may require delayed sternal closure in order to maintain hemodynamic stability.

The biliary portion of the case is deferred, and both the abdomen and chest are closed when it is most appropriate from a hemodynamic and bleeding standpoint. Important intraoperative management strategies include serial point of care acid-base and arterial blood gas/electrolyte monitoring, vigilant assessment of cardiac graft function using continuous transesophageal echocardiography, aggressive management of coagulopathy using serial viscoelastic testing, and intraoperative continuous renal replacement therapy in the event of acute renal dysfunction. Bleeding is well controlled in the operating room prior to bringing the patient back to the intensive care unit (ICU).

Intensive Care Unit (ICU) Considerations

The postoperative transplant care is best provided by the previously mentioned multidisciplinary team. The intensive care unit team is critical during the early perioperative period. The availability of around the clock intensivists with experience in the management of complex postoperative congenital heart disease patients and post CHLT concerns is essential. The ICU management of the post CHLT patient is focused on hemodynamic stability, appropriate ventilation,

correction of metabolic derangements, and management of hemorrhagic complications. Early neurologic assessment of these patient is critical given the inherent thromboembolic risk associated with this complex surgical procedure.

Periprocedural Concerns Post-CHLT

Due to the anatomic heterogeneity of single ventricle patients, it is inevitable that venous and arterial connections may not be in standard locations and often require surgical innovation to create necessary connections and reconstruct structures altered by abnormal development or previous palliative procedures. Therefore, it is essential that the congenital cardiac team remain involved and available, especially for the performance of post-transplant catheterization and biopsy procedures. It is common for patients to have developed areas of stenosis in the SVC, IVC, and pulmonary arteries that my require intervention at a future date with angioplasty or stenting. Furthermore, congenital cardiologists can aid in post-transplant biopsies particularly when the patient has had complex venous reconstructions. Additionally, patients who underwent aortic arch reconstruction such as a Norwood procedure may have residual issues requiring routine surveillance or stenting by an experienced congenital cardiac interventional cardiologist. The appreciation of the effects of immunosuppression and the risk of infection is a significant concern when this population presents for procedures. It is also advisable to communicate with the patient's care team when managing these patients for post-CHLT procedures to avoid perioperative complications and optimize care.

Conclusion

Patients presenting with failed, single ventricle physiology are a heterogeneous patient population with unique concerns and multisystemic consequences of their congenital heart disease. CHLT is the ultimate palliation for these patients and requires an experienced multidisciplinary team to coordinate their care, and to optimize outcomes and long-term survival.

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Heart Transplantation and Mechanical Circulatory Support in the Pediatric and Congenital Heart Patient

Shyamasundar Balasubramanya, Reshma M. Biniwale, and Glen S. Van Arsdell

Abstract

End stage heart failure in pediatric patients and patients with congenital heart disease (CHD) not treatable with maximum medical or surgical management may require surgical intervention in the form of heart transplantation and/or mechanical circulatory support (MCS) as a bridge to transplantation or bridge to recovery. The first human heart transplantation was performed by Christian Barnard in 1967. Since that time, the management of heart failure, mechanical circulatory support, and cardiac transplantation has advanced with significant evolution in heart failure medical management, donor selection, cardiac procurement, preservation techniques, implantation techniques, and perioperative management. Major progress in the care of this complex category of patients includes vital advances in immunosuppression regimens to ensure long-term allograft survival since the introduction of cyclosporine in 1983. The International Society for Heart and Lung Transplantation (ISHLT) registry was created in 1983 to collect and record data of heart transplant and MCS. Patient selection and recipient evaluation regarding candidacy for transplantation forms is vital to ensure optimal and successful outcomes. The world of MCS ranging from extracorporeal membrane oxygenation (ECMO) to ventricular assist devices (VAD) which range from the paracorporeal Berlin Heart EXCOR to the intracorporeal, intrapericardial HeartMate III represents a spectrum of devices available for utilization in patients needing to be bridged to heart transplantation.

Keywords

Heart transplantation · Mechanical circulatory support (MCS) · Ventricular assist device (VAD) · Extracorporeal membrane oxygenation (ECMO) · Cardiomyopathy Congenital heart disease

History of Heart Transplantation and Pediatric Heart Transplantation

The first human pediatric heart transplantation was performed by Adrian Kantrowitz at Maimonides Medical Center in Brooklyn, New York in an 18-day old neonate with severe Ebstein's anomaly of the tricuspid valve on December 6, 1967, using a normal heart from anencephalic neonate (Kantrowitz et al. 1968).

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The recipient survived for six and a half hours and later died secondary to severe metabolic and respiratory acidosis. This was the second heart transplant in the world and the first in the United States. It occurred three days after the first ever human to human heart transplant performed by Christiaan Barnard on December 3, 1967, at the Groote Schuur Hospital in Cape Town, South Africa on a 54-year-old dentist, Louis Washkansky, who survived for 18 days post-transplant before succumbing to pneumonia (Barnard 1967). The first human heart transplantation (xenotransplantation) occurred 3 years earlier in 1964 by James Hardy who transplanted a chimpanzee heart into a 68-year-old man with end stage heart failure (Hardy et al. 1964). Alexis Carrel and Charles Guthrie's pioneering work on suturing vascular structures in the early twentieth century paved the way for solid organ transplantation (Carrel 1907a, b; Carrel and Guthrie 1905, 1906). This work earned Carrel the Nobel Prize in Medicine and Physiology in 1912. Frank Mann and colleagues (Mann et al. 1933) at the Mayo Clinic and later Vladimir Demikov (Konstantinov 1998) at Moscow State University experimented on heart transplants in animals. Demikov performed the first orthotopic heart transplantation (OHT) in an animal heart in 1951 (Konstantinov 1998). The first successful pediatric heart transplantation was performed by Denton Cooley and colleagues in 1986 (Cooley et al. 1986). The first successful neonatal heart transplantation for hypoplastic left heart syndrome was performed by Leonard Bailey in 1985 (Bailey et al. 1986). The clinical outcomes were uniformly poor until the discovery of cyclosporine by Sandoz biologist Hans Peter Frey from a soil sample collected by a colleague. Although initially investigated as an antibiotic, Dr. Jean Borel realized cyclosporine's immunosuppressive potential and synthesized a pure compound, which he ultimately tested on himself. The introduction of cyclosporine in renal transplant in 1978–1979 introduced an era of calcineurin inhibitors in solid-organ transplantation in the 1980s with important positive results in heart transplantation (Colombo and Ammirati 2011). However, there were significant problems including high incidence of lymphoma, infection, and other causes of morbidity and mortality. When used as a drug combination along with prednisone in a study led by Dr. Thomas Starzl, there were markedly improved results in liver transplant patients. This helped the drug receive FDA approval in 1983 and it was later marketed under the brand name Sandimmune (Esquivel et al. 1987).

Current Pediatric Heart Transplant Landscape

In 1983, the International Society of Heart and lung Transplantation (ISHLT) Thoracic Registry was formed to collect multicenter pediatric and adult transplant data with data collection over the lifespan of the transplant patient and graft. The ISHLT 2019 registry (Anon 2019) report shows that currently there are 117 centers that perform pediatric heart transplants. The majority of these programs exist in North America and Europe. Another 21 centers reside in other non-European or North American sites. The United States accounts for 56 pediatric heart transplant centers (Anon 2019) (Figs. 1 and 2). Approximately, 73% of these transplants are performed by small volume centers which average 1–4 transplants per year. Ten percent of the cases are performed at large volume centers which are conducting more than 10 transplants annually.

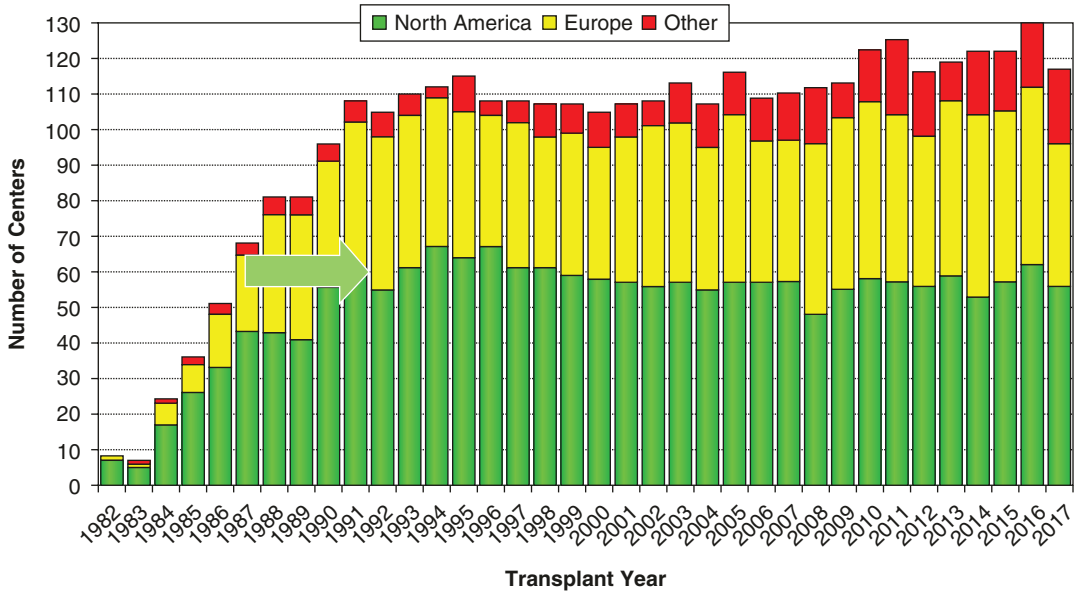

Fig. 1 ISHLT 2019 registry slides: The number of transplant centers reporting pediatric heart transplants (Anon 2019)

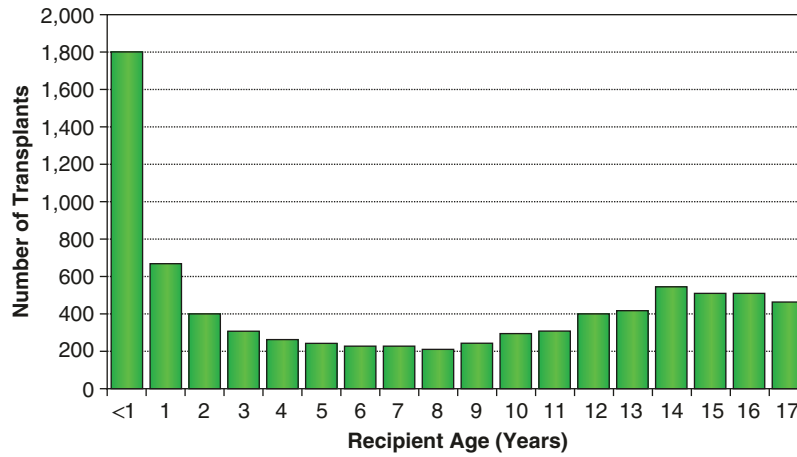

Fig. 2 Recipient age distribution of pediatric heart transplants from January 2005 to June 2018 (Anon 2019). ISHLT

Indications for Heart Transplantation and Recipient Characteristics

End-stage heart failure not treatable with conventional medical management will require heart transplantation as the only viable option to improve survival and quality of life. Rapid progression leading to non-survivable heart failure and cardiogenic shock will need bridging to heart transplantation by ventricular assist device (VAD) or by extracorporeal membrane oxygenation (ECMO). Unlike the adult population where left-sided VADs can be used as destination therapy in a select patient population in which transplantation is contraindicated, destination therapy is not available in children and young adults and can only be used as a bridge to transplant (BTT). Congenital heart disease and cardiomyopathy account for the vast majority of cases in children requiring a heart transplant. Children less than 1 year of age account for the largest number of

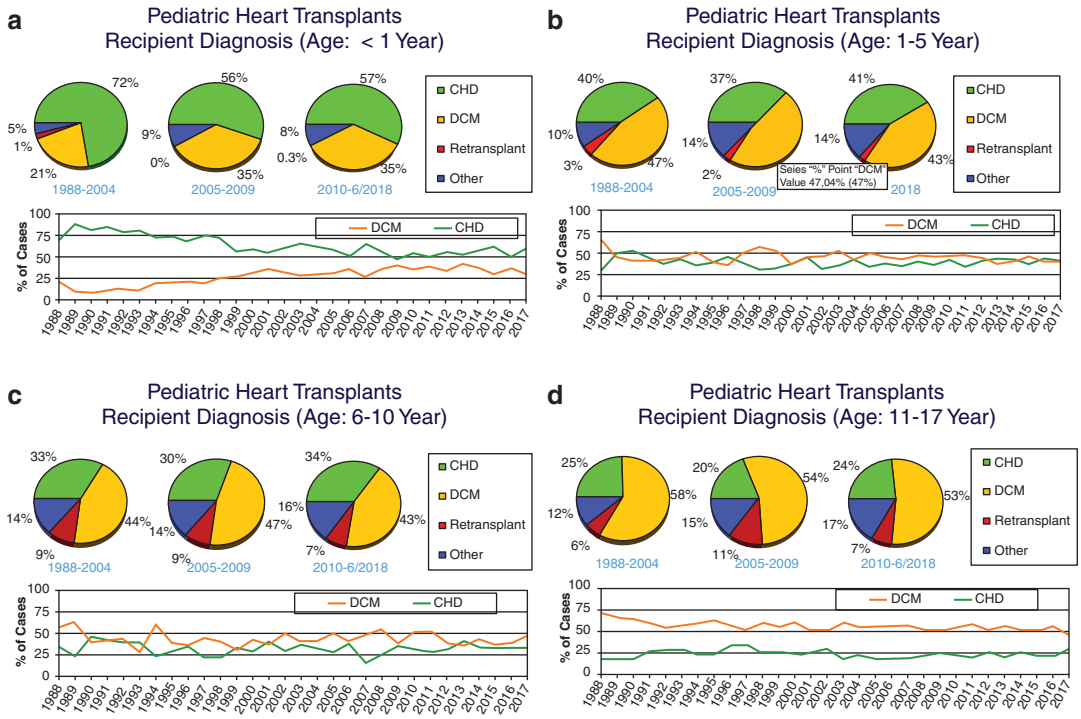

Fig. 3 ISHLT 2019 registry showing recipient diagnoses in different age categories (Anon 2019) (**a**—Age < 1 year, **b** Age 1–5 years, **c** Age 6–10 years, **d** Age 11–17 years)

heart transplant recipients (Fig. 3) (Anon 2019; Barnes and Gibson 2021). The ISHLT registry from 2019 (Anon 2019) shows that from 2005 to 2018, a total of 1800 children <1 year underwent heart transplants. In the less than 1 year age cohort, the most common cause of end stage heart failure requiring heart transplantation was congenital heart disease (CHD) (57%) followed by dilated cardiomyopathy DCM (35%) in the years 2015–2018 and CHD (72%) and DCM (21%) during the years 1988–2004 demonstrating the decreasing percentage of CHD as a cause for end stage heart failure (Anon 2019; Barnes and Gibson 2021; Kirk et al. 2020). This is further exemplified in all other age groups, where DCM is the leading cause of end-stage heart failure needing heart transplant. Retransplants accounted for <2% of recipients in the infant and younger age groups and 7–11% of recipients in the older age groups. Other causes (8–17%) included hypertrophic cardiomyopathy, restrictive cardiomyopathy, left ventricular noncompaction and arrhythmogenic right ventricular dysplasia cardiomyopathy. With the development and miniaturization of VADs, there has been a shift away from ECMO as the main form of mechanical circulatory support (MCS) as a bridge to heart transplant. While 53% of DCM recipients are bridged with a VAD, only 14.3% are bridged with a VAD to heart transplant (Anon 2019; Barnes and Gibson 2021; Kirk et al. 2020).

Heart Transplant Evaluation

All potential heart transplantation recipients go through an extensive pretransplant evaluation to assess the candidacy and medical fitness of heart transplantation. The main goal of this evaluation is to ensure long-term survival. While medical and surgical clearance is paramount, barriers from a social perspective are also comprehensively considered. Heart transplantation is offered to children who have end-stage heart failure that

cannot be meaningfully managed with medical treatment alone. However, if the patients have multi-organ system dysfunction, they will not be able to survive transplantation. A comprehensive evaluation of the underlying cardiac disease will include an echocardiogram, electrocardiogram, cardiac catheterization, and other studies such as computed tomography (CT), magnetic resonance imaging (MRI), and cardiopulmonary exercise testing in certain cases. Eliminating conditions that can be treated with a combination of surgical and medical therapy is vital to avoid the need for transplantation as in residual coarctation, anomalous left coronary artery from the left pulmonary artery, ventricular outflow tract obstruction, or undiagnosed arrhythmias. Anatomic details including systemic and pulmonary venous anomalies must be methodically delineated as they will impact the implantation strategy. Cardiac catheterization should include evaluation of pulmonary vascular resistance (PVR) which if elevated could result in right ventricular dysfunction in the donor heart after transplantation. A fixed PVR greater than 6 Wood units that is not reversible with pulmonary vasodilators including nitric oxide and a transpulmonary gradient of more than 15 mm Hg are relative contraindications to heart transplantation (Daftari et al. 2010). However, the use of mechanical circulatory support including VADs, chronic use of pulmonary vasodilators, and inotropes may decrease PVR over time and permit safe transplantation (Thangappan et al. 2021). Other organ systems including neurologic, immunologic, renal and gastrointestinal systems must also be comprehensively evaluated. The accepted contraindications to transplantation include the coexistence of any non-cardiac comorbidities that significantly shortens life expectancy compared with that expected with cardiac transplantation; or in conjunction with immunosuppressive requirements importantly reduces the expected survival after transplantation. Table 1 lists the specific contraindications.

Table 1 Specific contraindications to heart transplantation (adopted from Gajarski et al.) (Gajarski and Pearce 2007)

Active infection
Active ulcer disease
Coexisting active neoplasm
Renal insufficiency
Hepatic dysfunction with elevated transaminases
Recent pulmonary embolic event with infarction
History of recreational drug abuse
History of medical non-compliance

Sensitization

Sensitization involves formation of antibodies against foreign antigens exposed to the recipient's blood and immune system. Sensitization is a critical factor that can affect heart transplant outcomes and is followed by the ISHLT registry. Every recipient's blood is tested for panel reactive antibodies (PRAs) to determine any inability to accept specific donors as acute rejection would be the unfortunate outcome. This is usually defined as a calculated percentage of the population that is excluded as donors for a specific recipient. Any PRA value >10% is considered sensitized. There has been an increase of patients with significant PRAs with time as shown in Fig. 4a. Children with CHD have higher PRA values than (Fig. 4b) children with DCM. The exposure to blood products from previous surgeries, VAD placements and homograft material are thought to elicit the immune response that results in significant antibody formation and elevated PRAs. Preformed and post-transplant donor specific antibodies (DSA) are associated with antibody mediated rejection (AMR). These antibodies along with complement fixing antibodies correlate with complement deposition on the graft and higher risk of AMR. Acknowledgement of this process may allow the utilization of personalized immunotherapy which targets the complement mediated rejection (Zhang et al. 2018).

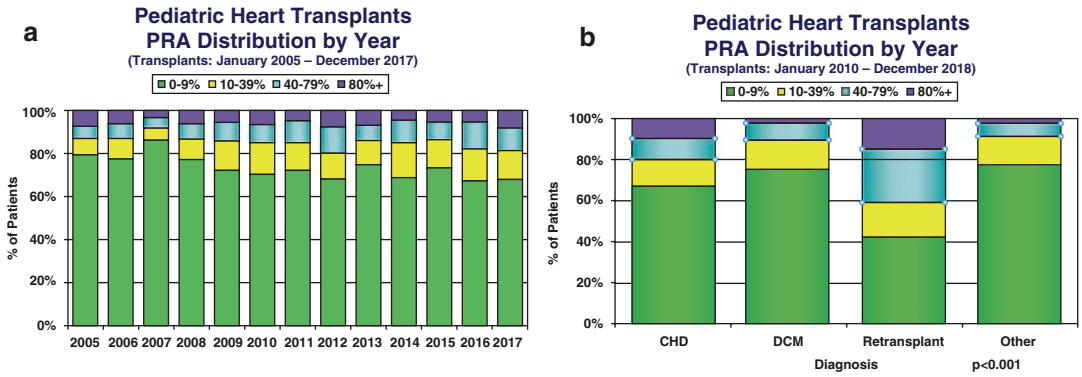

Fig. 4 ISHLT 2019 Registry Slides showing Panel Reactive Antibodies (PRA) distribution by year (**a**), Diagnosis (**b**) (Anon 2019)

Waitlist Mortality

Existing waitlist mortality varies by country, region, and institution. There are many published reports from large national and international data sets that have consistently reported waitlist mortality between 17% and 30%. The current reported waitlist mortality in the United States is 17%. The waitlist mortality for patients with CHD (22%) is higher than in children with DCM (8–14%). The waitlist mortality in Australia is 22% and Eurotransplant 18% (Kirk et al. 2020).

Ischemic Times

Ischemic times (IT) greater than 4 h have been associated with prolonged intensive care unit and hospital stays and early phase graft failure (Kirk et al. 2020). The largest cohort of pediatric heart transplant patients (n = 4716) retrospectively evaluated over 20 years showed that an IT less than 3.5 h was associated with the best outcomes. The 2017 ISHLT registry report focused on IT that varied by geographic region, recipient age, diagnosis, mechanical support, and acuity. An IT greater than 4 h compared with 2–4 h was found to be an independent risk for decreased survival at 1 year (87% vs 92%) and 5 years (77% vs 82%) but there was no long-term effect on mortality. The use of cardiac preservation solutions has also evolved, with University of Wisconsin (UW) solution being the predominate source of cardiac preservation in approximately 40% of donors (regions 1,2,5,9,10,11). However, Custodiol (HTK) is preferred in regions 6, 7, 8 and Celsior in region 4 for pediatric heart transplantation. Currently, Del Nido solution has been used in adult donors after circulatory death (DCD) and Custodiol is used commonly in Europe as well as in ex vivo Organ care systems (OCS) (TransMedis Inc). There were no significant differences in survival outcomes or rejection episodes following the use of different preservation solutions observed in the pediatric population (Shaw et al. 2020).

Donor Management and Donor Heart Procurement

Donor cardiectomy is performed most commonly in the medical centers where the donor was declared brain dead or sometimes in dedicated procurement centers managed by the organ procuring organizations (OPO). Optimal donor management in the intensive care unit (ICU) and the operating room (OR) during the recovery process forms a vital component of the procurement and is necessary for optimal donor heart function. The goal should be to achieve hemodynamic stability with adequate end organ perfusion, electrolyte balance, and urine output. Early and focused management of the potential donor can increase

the number of available donor hearts with improved post-transplant outcomes. All donors should have a continuous arterial line blood pressure measurement and a central venous line pressure measurement. Hypovolemia that results from brain death and consequent diabetes insipidus must be managed with crystalloid administration and can be supplemented with colloid. Hemoglobin levels should be maintained greater than 7 g/dL. Up to 80% donors have significantly reduced circulating levels of arginine vasopressin resulting from compression of the pituitary gland during brain herniation. Vasopressin is typically administered in donors with neurogenic hypotension refractory to fluid resuscitation. The mean arterial pressure should be maintained greater than 60–70 mmHg.

After median sternotomy, a pericardial well is created. The entire ascending aorta is dissected from its attachments to the pulmonary artery and the posterior pericardium. The superior vena cava is dissected circumferentially and freed from its attachments from the right pulmonary artery and the azygous vein is ligated and divided. When the thoracic and abdominal organ procurement teams are ready for cross clamping, the donor is systemically heparinized with intravenous unfractionated heparin. A cardioplegia catheter is placed in the ascending aorta for administration of a suitable preservative solution containing high potassium concentration with the goal of obtaining a diastolic arrest of the heart. At our institution, we use the UW during the procurement process. Other frequently used solutions used include Celsior, Custodial, and Del Nido solutions. The left atrium is vented by incising the left inferior pulmonary vein or the left atrial appendage (when the lung is concurrently being procured). The right atrium is vented by hemitransecting the inferior vena cava (IVC) at the level of the cavo-atrial junction just above the diaphragm. The ascending aorta is cross clamped just proximal to the innominate artery takeoff and 1–2 L of the preservation solution is administered into the ascending aorta via the cardioplegia catheter at a pressure of 70–80 mmHg. Topical slushed ice is placed over the heart to further induce topical cooling of the heart. Once the preservation solution is fully administered, the IVC is completely transected at the level of the diaphragm, the LA is split (if the lung is being concurrently procured) and an adequate LA cuff is fashioned out for implantation. The SVC along with the innominate vein is taken with the heart. The PA is split just before its bifurcation into the branch pulmonary arteries (if lung is being concurrently procured) or taken along with the branch PAs. The aorta is transected just before the innominate artery takeoff after removing the cross clamp and thus completing the donor cardiectomy. In patients with CHD, often times the recipient needs aortic arch augmentation and consequently the entire aortic arch needs to be harvested. The SVC is harvested along with the innominate vein should the recipient have a left superior vena cava (LSVC) that needs to be redirected to the right atrium. This is accomplished by connecting the innominate vein to the LSVC. Once the donor cardiectomy is completed, the heart is placed in cold preservation solution within a plastic bag and packaged with 2 additional layers of plastic bags with slushed ice to maintain hypothermia during its transport to the recipient institution for the implantation.

Adult Congenital Heart Disease and Heart Transplant

The percentage of patients with CHD surviving to adulthood has approached 95%. Although survival has improved significantly, many congenital heart disease patients are left with residual cardiac lesions and a palliated physiology with resultant morbidity and mortality. Adult congenital heart disease (ACHD) patients are at high risk for the development of advanced heart failure (HF) from the combination of palliated cardiac anatomy, pathologic remodeling from persistent hemodynamic abnormalities and the lack of adequate medical therapies to mitigate the progressive ventricular dysfunction. The population increase of ACHD patients with heart failure is reflected by the increase in the number of patients requiring advanced therapies for end-stage disease and the number of ACHD patients which are

increasingly referred for heart transplantation (HT). While late post-heart transplant outcomes are often better in ACHD patients, higher perioperative mortality is seen due to the multisystemic consequence of CHD. As a result, multi-organ dysfunction particularly in the single ventricle population is increasingly considered. Due to the heterogeneity in the ACHD population, the presentation of heart failure can vary dramatically. Patients with complex forms of ACHD often fail to exhibit signs and symptoms classically associated with ventricular dysfunction. A lifetime of abnormal cardiac anatomy and physiology can lead to compensatory mechanisms that result in the absence of classic physical exam findings (Lewis and Rosenbaum 2018).

The presentation of HF can vary dramatically in ACHD patients due to the physiologic heterogeneity. Simple anatomic forms of ACHD such as isolated valvular heart disease or repaired shunting lesions may present with similar HF symptoms as the general population. However, complex ACHD patients often fail to manifest signs and symptoms usually associated with ventricular dysfunction. Patients with complex congenital heart disease, particularly those with single ventricle variants, may not manifest changes in cardiac output on examination because of chronic systemic venous hypertension. Established metrics of cardiac function may not be accurate in all patients with ACHD. Despite varied presentations, HF remains a common clinical diagnosis in the ACHD population. Hemodynamic evaluation with cardiac catheterization is often necessary to determine the presence and severity of HF in ACHD patients.

ACHD patients are at a two- to threefold increased risk for intraoperative and early mortality when compared to the general population. The most common cause of death in the early post-HT period was primary graft dysfunction (PGD). Increased ischemic times due to procedural complexity, elevated pulmonary vascular resistance and allosensitization may all increase the risk of PGD in the ACHD cohort. ACHD patients also show increased rates of death from hemorrhage, renal failure, and multi-organ system dysfunction. Because the majority of ACHD patients require additional surgery to correct residual anatomic abnormalities at the time of transplant, bypass time and ischemic times can be longer and can lead to worsening coagulopathy and massive transfusion, prolonged intubation and increased risk for infection. ACHD patients undergoing transplant frequently have a physiologic substrate of hepatic and endothelial dysfunction from prolonged cyanosis and elevated systemic venous pressures that can significantly increase the impact of long bypass and ischemic times.

The ACHD Patient with Systemic Right Ventricle (SRV), Single Ventricular Physiology

The SRV exists in many variants of ACHD and encompasses patients with single and biventricular circulation. Overall, the prognosis of the SRV is highly variable, with some patients requiring HT in their second and third decades and others achieving a near normal existence. SRV often presents similarly to patients with HF and a morphologic left ventricle. However, prolonged exposure to systemic pressure and residual lesions can induce a variety of abnormalities dependent on each patient's unique anatomy and prior repairs, complicating clinical assessments. The unique structure of the SRV, the presence of muscular bands, and the high incidence of hypertrophied trabeculations make accurate delineation of SRV function complex. In all patients with SRV and HF, delineating the degree of systemic tricuspid regurgitation is necessary. Because patients with congenitally corrected transposition of the great arteries may present with an Ebsteinoid tricuspid valve, early repair, and replacement should be considered when symptoms or severe regurgitation is present, prior to the onset of decreased SRV ejection fraction. Ultimately HT will be required in a subset of SRV patients.

Eisenmenger's Syndrome and Combined Heart–Lung Transplant

The role of heart and lung combined transplant for Eisenmenger's syndrome and certain patients with complex ACHD and pulmonary hypertension remains controversial. Combined Heart–Lung transplant remains the definitive treatment for Eisenmenger's syndrome, accounting for nearly one-third of all combined heart–lung transplants to date. However, low average life expectancy post-combined heart–lung transplants (<4 years) have created controversy regarding its role due to limited organ availability and the low 4 year survival rate.

Anatomic Variability and Heart Transplantation in the Failing Fontan Patient

CHD patients present with additional surgical challenges in contrast to DCM patients. They can have variability in size or numbers of cardiac chambers. The great vessels can be hypoplastic, switched, or have been augmented with homograft. The majority of CHD patients would have had palliative or corrective heart procedures as the initial approach to treatment. The prior operations can result in significant adhesions or anastomotic stenoses. They may add increased ischemic time and morbidity to the transplant due to other anatomic anomalies that need to be addressed at the time of the transplant. Examples include aortic arch reconstruction using donor aorta under deep hypothermic circulatory arrest (DHCA) or pulmonary patch arterioplasty needed in patients with stenotic pulmonary arteries or PA stents that require removal and patch arterioplasty. Situs inversus or persistent LSVC can pose challenges in redirecting venous blood. Recipients who have had hypoplastic left heart syndrome and a Norwood Stage I procedure rarely require DHCA for an arch procedure, but may require PA augmentation at the shunt site. After the bidirectional Glenn, the SVC is often foreshortened due to its anastomosis with the RPA. This can be accommodated by utilizing a larger length of the donor SVC. If the left sided SVC is present, it can be routed to the RA using the donor innominate vein or a synthetic graft. Significant improvisation and surgical technical skill are required to address the previously palliated anatomy when preforming a heart transplant in the complex ACHD patient.

The majority of single ventricle patients who ultimately need a heart transplant have failing Fontan physiology. These patients pose a significant challenge for heart transplantation. Most Fontan patients would have undergone at least 2–3 prior sternotomies making re-entry more of a surgical risk factor. Most patients would have developed many aortopulmonary collateral vessels that result in a large shunt, volume overload and risk of severe bleeding. There is a need for supraphysiologic cardiopulmonary bypass flows and increased pulmonary venous return that impairs surgical visualization, especially during the left atrial anastomosis. Left atrial venting will become a necessity to prevent rapid rewarming during the performance of the other anastomoses. These collaterals can be coiled by the interventional cardiologist in the cardiac catheterization laboratory prior to transplant (Tan et al. 2021). Failing Fontan patients also have poor metabolic and nutritional status due to supraphysiologic central venous pressures which may result in protein losing enteropathy (PLE), Fontan associated liver disease (FALD) or congestive hepatopathy, ascites, plastic bronchitis, lymphatic abnormalities, and edema.

Fontan Heart Failure Classification

- Type 1 heart failure in Fontan patients is also called Fontan failure with diminished ejection fraction. It is the most common type seen in children and it presents with consistent signs and symptoms of heart failure with reduced EF, such as pulmonary edema, hepatic congestion, and ascites. This closely resembles systolic heart failure in patients with two ventricles.
- Type 2 heart failure in Fontan patients, known as Fontan failure with preserved ejection fraction, presents with a preserved ejection frac-

Table 2 Hemodynamic phenotypes of Fontan failure (Book et al. 2016)

Phenotype	Systolic function	Ventricular end-diastolic pressure	Cardiac output	SVR
Type I FFrEF	Reduced	Elevated	Normal or low	Elevated
Type II FFpEF	Normal	Elevated	Normal or low	Elevated
Type III FFnH	Normal	Normal	Normal or elevated	Normal or low
Type IV FFaL	Normal	Normal or low	Normal or elevated	Normal or low

tion, with signs and symptoms of pulmonary venous congestion and congestive hepatopathy, with elevated venous pressures. This type of heart failure in some way mirrors HFpEF in patients with two ventricles.

- Type 3 heart failure in Fontan patients, also known as Fontan failure with normal pressures, presents with right-sided congestion, such as hepatosplenomegaly, ascites, and portal venous outflow obstruction, but with normal ejection fraction and hemodynamics. Multisystem organ failure in the setting of good hemodynamics is frequently seen, making it challenging to treat.
- Type 4 heart failure in Fontan patients, known as Fontan failure with abnormal lymphatics, will present with normal hemodynamics, but signs and symptoms of lymphatic failure, such as plastic bronchitis and protein-losing enteropathy. Patients will often have normal Fontan hemodynamics (Book et al. 2016) (Table 2).
- FFrEF, Fontan failure reduced ejection fraction; FFpEF, Fontan failure preserved ejection fraction; FFnH, Fontan failure normal heart; FFaL, Fontan failure abnormal lymphatics; SVR, systemic vascular resistance.

Implantation

There are three described surgical techniques for orthotopic heart transplantation (Barnes and Gibson 2021). The bi-atrial technique was initially described in the 1960s and was predominately used into the 1990s. The bi-atrial technique involves the anastomoses of the left atrium (LA), right atrium (RA), Aorta (Ao), and pulmonary artery (PA) of the donor with the recipient. Although technically relatively simple, concerns regarding atrial dysfunction, conduction disturbances, and atrioventricular valve dysfunction led to the adoption of the bi-caval technique introduced in the 1990s. This bi-caval technique preserves the donor RA and is the most commonly practiced technique today. It encompasses 5 anastomoses between the donor and recipient LA, Aorta, PA, inferior vena cava (IVC) and superior vena cava (SVC). The third technique described in the 1980s is similar to the bi-caval technique, but also preserves the donor LA by anastomosing the right and left pulmonary veins separately and preserving the bridge of tissue between them. Since it is technically more challenging and time consuming, it is not as widely utilized as the other two techniques.

Special Circumstances

Outcomes of Heterotaxy patients after Heart Transplantation with Complex Venous Reconstruction were reviewed at our institution over a period of 8 years. A total of 1625 heart transplant recipients were identified during the study period: 18 (1.1%) in Group A (complex venous reconstruction) and 1607 (98.9%) in Group B (no-reconstruction). Survival (1 month, 1 year, 5 years, 10 years) was: Group A (89%, 83%, 52%, 52%) and Group B (96%, 87%, 73%, 56%). There was no significant survival difference (log rank, $p = 0.36$). Unadjusted HR for all-cause mortality was 1.47 (CI 0.66–3.30, $p = 0.34$). Adjusted multivariate analysis showed HR 1.16 (CI 0.36–3.75, $p = 0.81$) (Biniwale et al. 2014).

Postoperative Management

There are vital treatment considerations in the postoperative care of pediatric transplant patients. Primary graft dysfunction (PGD) is a devastating

complication that occurs in 2.4–28% of the pediatric transplant population (Dipchand et al. 2015; Rossano et al. 2016). PGD occurs in the immediate postoperative period and is generally defined as significant when the ejection fraction is below 40%, there is a need for high inotropic support, or a need for mechanical circulatory support (Rossano et al. 2016). Contributing factors in the development of PGD, include donor characteristics of age and death and recipient characteristics of elevated pulmonary vascular resistance (PVR), organ dysfunction, mechanical ventilation and mechanical support, and procedural variables including longer ischemic time and smaller center volume (<5). Outcomes are poor especially if mechanical support is needed for longer than 4 days with an overall 3-year survival of 54% being reported (Rossano et al. 2016).

Treatment for high PVR and right ventricle protective strategies need to be initiated in the intraoperative period and extended into the postoperative period. Right ventricular failure is an ominous complication and can be seen in up to half of the recipients and has been shown to be the cause of death in 19% (Bozbaş et al. 2013; Matthew et al. 2018). The causes of RV failure in the transplanted heart, include pulmonary hypertension in the recipient, longer ischemic times, and reperfusion injury. The most effective therapies for RV dysfunction include decreasing the PVR with inhaled vasodilators (nitric oxide) or oxygen, afterload reduction with phosphodiesterase inhibitors like milrinone and sildenafil, inotropic support, higher heart rate (atrial pacing) and optimal fluid balance (Bozbaş et al. 2013; Matthew et al. 2018).

Another aspect of postoperative heart transplant care is the lack of parasympathetic innervation. The transplanted hearts lack the tachycardic response to hypotension or hypovolemia. To achieve adequate heart rate either isoproterenol working on adrenergic receptors and/or epicardial pacing is often used. These can be discontinued after the underlying rhythm is adequate. Occasionally, a permanent pacemaker may need to be implanted if there is damage to the sinus node of the donor graft due to anatomic or preservation injury. Dual sinus node function may be seen in biatrial anastomoses. Transcatheter ablation of the redundant sinus node may be later preformed.

Immunosuppression management is a vital component of postoperative treatment after heart transplantation. There are 2 phases of immunosuppression—the induction phase (given intraoperatively) and maintenance therapy (given daily for the recipients' lifespan). There are many regimens used, but the most currently used is a combination of tacrolimus and mycophenolate mofetil. In redo heart transplant patient, a renal sparing immunosuppressive protocol with sirolimus or everolimus is frequently employed.

Outcomes

There are many potential complications that may occur after heart transplantation. The primary challenges are rejection, infection, and cancer. A multidisciplinary heart transplant team is required to care for patients with specific protocols to monitor for these complications and treat when necessary. Outcomes at 1 year and 5 years have improved in comparing 1982–1991 (1 year = 72.1%; 5 years = 60.6%) to 2010–2017 (1 year = 91.5%; 5 years 83%). Based on data from 2002 to 2009, the current 10-year survival is 68% with 15-year survival at 58.9%. Looking at 10-year survival by age categories, patients transplanted between ages <1–10 years old had no statistical difference between all of these age groups and those patients 11–17 years old with a 10-year survival of this group of 70.2%. Comparing outcomes across ages based on etiology of the transplant, those patients with DCM had higher survival (1 year survival 91–93%) versus CHD (82–88%) (Barnes and Gibson 2021).

Mechanical Circulatory Support in the Pediatric Population

Ventricular assist devices (VADs) have become an vital therapy for children with end-stage heart failure, with increasing utilization over the past

Fig. 5 Berlin heart device EXCOR

decade. VADs are used as a bridge to heart transplantation in this patient population. Destination therapy is not available in the pediatric population (Morales et al. 2020). The three currently available and approved VADs in the United Sates are the pulsatile paracorporeal Berlin Heart, Pediatric device (EXCOR) (Fig. 5) available in various volumes for implantation either as a LVAD or a right ventricular assist device (RVAD), the continuous flow magnetically, levitated and intrapericardially implantable HeartMate III (Abbott) for older children and the percutaneously inserted continuous flow (CF) Impella LVAD (Abiomed) (Figs. 6 and 7) inserted percutaneously or via arterial cutdown. The EXCOR has been the main pediatric device utilized and remains an important tool for many pediatric patients. This device was approved under Humanitarian Device Exemption status in 2011 and received post-market approval (PMA) in 2017 from the Food and Drug Administration (Morales et al. 2020). The immediate fundamental aim of VADs is to provide hemodynamic stability for a failing circulation that is not responsive to maximum medical management. Consequently, VAD should be preferably implanted before the development of severe end-organ dysfunction in order to optimize the outcomes. The goal is to improve tissue and organ perfusion, improve the quality of life and waitlist survival. The majority of heart transplant centers in the United States implant less than 10 VADs per year. The 2019

Fig. 6 Impella device Abiomed

ISHLT registry report shows that there is an increasing trend toward using VADs as a bridge to transplant (BTT) with currently over one-third of patients that undergo a heart transplant requiring a bridge to transplant with a VAD.

The optimal timing for the VAD placement is decided by an assessment of the potential risks and benefits of the intervention. Numerous considerations determine this; including the VAD risk profile: the patient age/size, anatomy, multi-organ function and device type, and factors related to illness severity and comorbidities. Paracorporeal devices are frequently placed in younger, smaller patients with end-stage disease, CHD and multi-organ system comorbidities at the time of VAD implantation. The most recent PEDIMACS report reveals that one-third of patients are in the INTERMACS Profile 1 at the

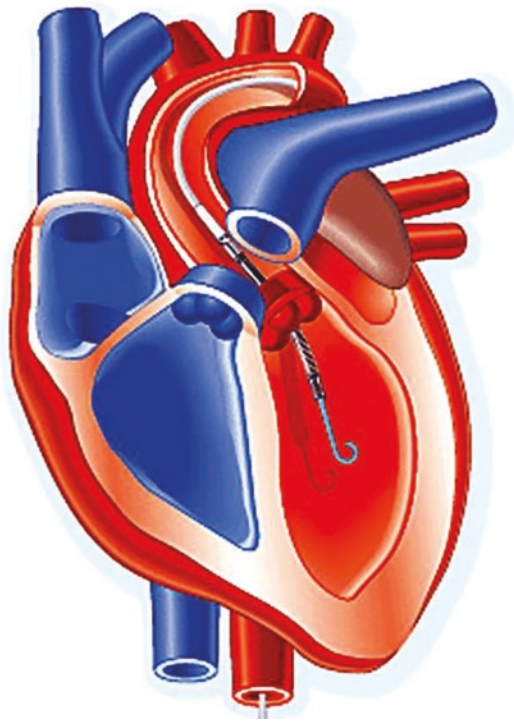

Fig. 7 Impella anatomic placement

time of implantation including 40% of patients receiving paracorporeal devices, 49% of patients receiving paracorporeal, pulsatile devices, and 19% of patients receiving intracorporeal, continuous-flow devices (Morales et al. 2020).

Indications for VAD

1. *Failure of Medical Management*: Despite maximal medical therapy, inadequate cardiac output, and tissue perfusion, results in liver dysfunction, renal dysfunction, feeding intolerance, and progressive respiratory decompensation develops. Multi-organ system dysfunction is common in the pediatric VAD patient prior to VAD placement with 45% of patients requiring mechanical ventilatory support. (paracorporeal devices 75–85% of patients compared to intracorporeal devices 21%), 94% on inotropes, 64% requiring feeding tubes/TPN, 40% with hyperbilirubinemia, and 30% having glomerular filtration rate (GFR) < 60 mol/min/1.73 m^2.
2. *Post-cardiac Surgery, Failure to Wean from Cardiopulmonary Bypass* (*CPB*): The existence of a previous sternotomy and/or previous cardiac surgeries in pediatric VAD patients ranges from 23% to 39%. Post-cardiac surgical patients who fail to wean from CPB are likely to be placed on ECMO or temporized with paracorporeal CF devices.
3. *Uncontrolled Arrhythmias*: Cardiogenic shock from arrhythmias is rare and in some cases may require ECMO support. VAD support is needed in 10% of pediatric patients with arrhythmias unresponsive to medical therapy.
4. *Bridge to Transplant*: The primary indication for VAD in North America is bridge to transplant (BTT) with 55% of patients listed for HT at the time of VAD implantation and 34% being evaluated for organ transplant candidacy. Occasionally, VADs are used as a bridge to recovery (6%) or destination/chronic therapy (DT) (2%) and other (3%).

Ventricular Assist Device Selection: The devices available for pediatric patients with end-stage HF can be classified in several ways (Table 3). They can be classified according to duration of therapy (temporary or durable) or by design and function—pulsatile flow (PF) or continuous flow (CF) or by site of implantation (paracorporeal, extracorporeal, intracorporeal, or intravascular) and by the form of circulatory support they provide [LV, RV, SV, BiV, or total artificial heart (TAH)].

Pulsatile Flow Devices: The Berlin Heart EXCOR (Berlin, Germany) is a pneumatically driven paracorporeal VAD which has been the most commonly used device for ventricular support throughout the world for the past 20 years. In the United States, the EXCOR is the only FDA approved VAD for pediatric patients that comes in a number of sizes which facilitates support of pediatric patients across a very broad range of weights (3 kg and greater) (Fig. 8).

Table 3 Devices used in children and adolescents (Lorts et al. 2021)

Device	Manufacturer	Output	Configuration
Short Term VAD			
RotaFlow	Getinge	up to 10 LPM	RVAD/LVAD/BIVAD
PediMag	Abbot	up to 1.5 LPM	RVAD/LVAD/BiVAD
CentriMag	Abbot	up to 10 LPM	RVAD/LVAD/BIVAD
TandemHeart	LivaNova	up to 5 LPM	RVAD/LVAD/BIVAD
Tandem Life Protek Duo	LivaNova	up to 4.5 LPM	RVAD
Impella 2.5, 5.0, 5.5	Abiomed	up to 2.5-5.5 LPM	LVAD
Impella RP	Abiomed	up to 4.0 LPM	RVAD
Long Term VAD/TAH			
Berlin Heart EXCOR	Berlin Heart	.6-8 LPM	RVAD/LVAD/BIVAD
HeartMate 3	Medtronic	up tp 10 LPM	LVAD
Jarvik 2015	Abbot	.5-3 LPM	trial ongoing
SynCardia TAH 50cc	SynCardia	up tp 7.5 LPM	BIVAD

The Syncardia total Artificial Heart (TAH, Tucson, Arizona, USA) is a pulsatile durable device that is intracorporeal and pneumatically driven and provides biventricular support following cardiectomy. It has played a role in the CHD and pediatric population in a variety of situations including graft failure post-transplant and support of complex CHD including the Fontan circulation. There are two sizes which are FDA approved, one with a 70 mL chambers and the other with a 50 mL chambers. The smaller device is used in patients with a body surface area (BSA) < 1.5 m^2. This device requires resection of both ventricles for implantation and is obviously not used as a bridge to recovery. One of the limiting factors in the use of this device is the ability to close the chest after implantation and therefore chest size is a significant limiting factor.

Continuous Flow Devices: There are multiple paracorporeal, temporary pump heads are available. The most commonly used pumps are the RotaFlow (Maquet) centrifugal pump and the Centrimag/Pedimag (Abbott Laboratories) magnetically levitated devices. These may be implanted only as bridge to transplant or bridge to recovery. The TandemHeart is an intravascular device connected to a centrifugal pump that can be placed percutaneously and intravenously to support the RV with ejection to the pulmonary artery (or the LV through a trans-septal approach) and has been used in pediatric patients as an extracorporeal device for LV support and single ventricle (SV) support. The Impella (Abdiomed) device is available in multiple sizes is also an intravascular device with an axial pump designed to be placed across the aortic valve and into the LV to allow short-term ventricular support.

Of the multiple, intracorporeal, durable devices, the one that can be utilized in larger pediatric patients and adolescents is the HeartMate III (Abbott Laboratories, IL, USA) (Fig. 9), which is a centrifugal fully magnetically levitated device. This device is used for long-term, durable support and is available for patients who are generally greater than 15–20 kg.

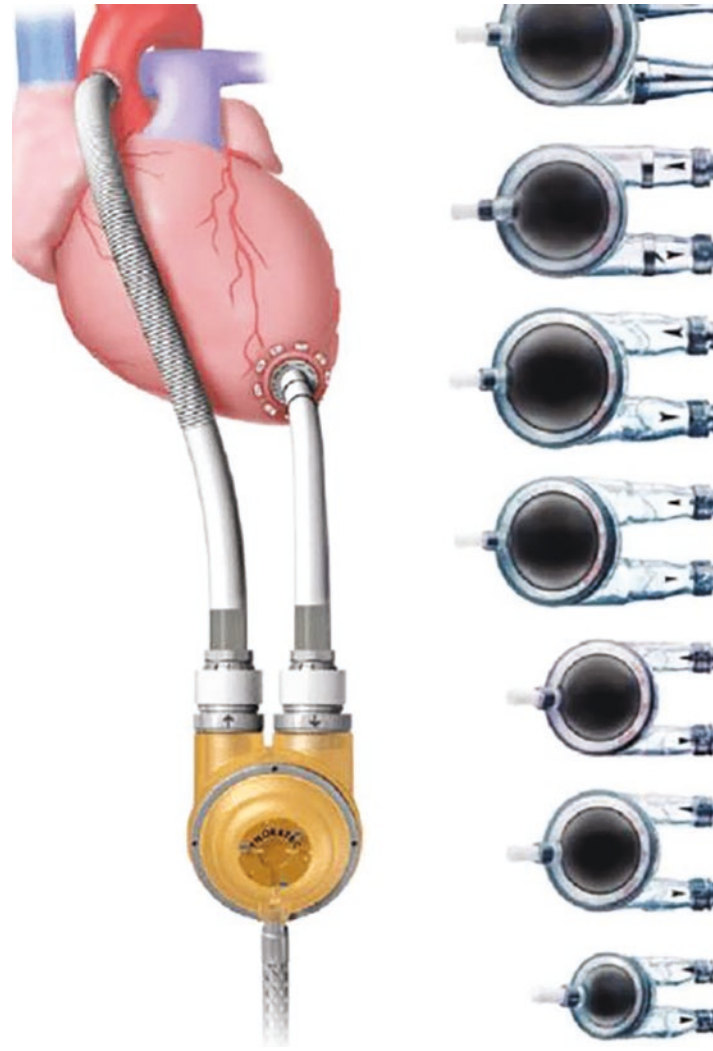

Fig. 8 Berlin heart in multiple sizes

Operative Management of Ventricular Assist Devices

Achieving an ideal inflow configuration is vital in the implantation of these devices. The guiding principle for all VAD implantations whether intracorporeal or paracorporeal is to position the inflow cannula parallel to the interventricular septum and facing the systemic atrioventricular valve. Apical cannulation is recommended for dilated ventricles, but in hypertrophic cardiomyopathy and restrictive cardiomyopathy the apical cannulation might not be appropriate and left atrial cannulation may be preferred. The outflow cannula is generally anastomosed to the ascending aorta with an interposition graft. For RVAD placement, there are 3 potential anatomic sites including the: (1) right atrium (standard site for EXCOR), (2) diaphragmatic wall, and (3) free RV wall.

In the early perioperative period, anticoagulation is essential to avoid device thrombosis and stroke and is initiated as soon as possible. The newest anticoagulation regimen using a bivalirudin-based protocol has dramatically decreased the incidence of thromboembolic events previously seen with heparin use in Berlin heart recipients (Iyengar et al. 2017).

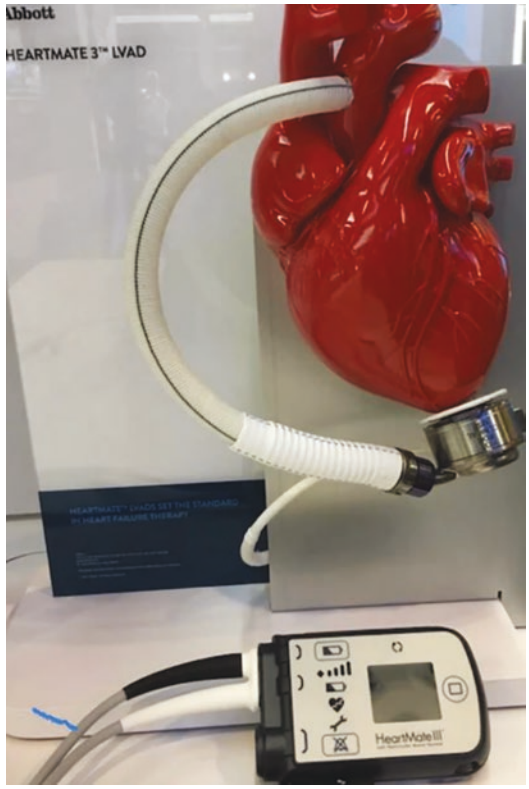

Fig. 9 HeartMate III

Summary

Heart transplantation is the gold standard treatment in pediatric and adult congenital heart patients with end-stage cardiomyopathy and heart failure. Heart transplantation has evolved significantly since its inception and the introduction of therapeutic immunosuppressives. The incorporation of DCD (donation after circulatory death) heart donors in the future will likely amplify the donor pool and increase the number of transplants overall and decrease death due to prolonged waitlist times due to donor availability. Bridging these patients with the utilization of mechanical circulatory support in the form of durable intracorporeal or temporary paracorporeal VADs and ECMO have decreased the waitlist mortality and are an invaluable therapeutic option in patients who have a long wait time but have exhausted all medical therapeutic options and face cardiac decompensation.

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Anesthetic Considerations for Pediatric Cardiac Hybrid Procedures

Christine T. Trieu, Moris M. Salem, and Sanjay Sinha

Abstract

Advancements in both surgical and interventional cardiology since their inceptions have led to improve prognosis and survival for patients born with congenital heart defect (CHD). Treatment options for these patients have expanded with continual development and innovations in both these fields independently and as a hybrid field. Cardiac hybrid procedures for CHD pose many unique challenges with regard to the anesthetic management of these patients. A systematic, thorough, and individualized anesthetic approach is a critical component of a multispecialty collaboration.

Keywords

Hybrid · Hybrid procedure · Congenital heart disease · Hybrid anesthetic consideration Pediatric hybrid management

Preoperative Assessment

The preoperative assessment of a patient, pediatric or adult, undergoing a proposed hybrid procedure for congenital heart defect (CHD) is complex and challenging in many aspects for the anesthesiologist caring for these patients. The ultimate goal of a hybrid procedure for CHD is to minimize risk and optimize outcome and recovery (Brodt 2018). A comprehensive understanding of both the patient's CHD and the unique intricacies of the combined surgical and interventional cardiology procedure is essential in providing a safe anesthetic in this patient population. Thus, the preoperative anesthetic evaluation must take into consideration both the patient and procedure-specific aspects.

Patient Considerations

No anesthetic agent of choice is appropriate for all patients with CHD undergoing a cardiac hybrid procedure. However, the anesthetic plan for all will be general endotracheal anesthesia

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(GETA). The anesthesiologist caring for these patients must comprehend the risks, underlying anatomy and pathophysiology, and the effects of the anesthetic strategy chosen on the patient's hemodynamic status. Patients who undergo a hybrid procedure for CHD vary greatly in age, ranging from neonates to adults, from complexity and physiology of underlying cardiac lesion, from current hemodynamic stability, and cooperation capabilities (Odegard et al. 2016a, b). There is no one size fits all approach. Therefore, an individualized and systematic approach is recommended.

First and foremost, a complete history and physical examination with a particular focus on the cardiovascular and cardiopulmonary status are necessary. It is important to note certain specific cardiac defects with increased anesthetic risks, such as single ventricle physiology, pulmonary arterial hypertension, and left ventricular outflow tract (LVOT) obstruction (Odegard et al. 2016a, b). The patient's functional status and/or assessment of cardiopulmonary reserves should be investigated.

All available, recent, and relevant imaging including chest radiograph (x-ray), echocardiogram, cardiac catheterization, cardiac computerized tomography (CT) scan, and cardiac magnetic resonance imaging (MRI) must be reviewed to better understand the patient's anatomy and physiology. A baseline electrocardiogram (EKG) needs to be assessed for underlying rate and rhythm. Recent and relevant laboratories, such as complete blood count (CBC), chemistry panel, coagulation panel, and type and screen, should be evaluated. All cardiac medications should be reviewed and continued as indicated.

The American Society of Anesthesiologists (ASA) nil per os (NPO) guidelines should be followed unless the procedure is emergent. These patients should be prioritized in terms of procedure time to limit their NPO time, especially young or single physiology patients. Separation anxiety is likely in pediatric patients who are older than 6 months of age. Additionally, younger pediatric patients are also likely to be uncooperative compared to older or adult patients. Premedication via oral (PO), intravenous (IV), intranasal (IN), or intramuscular (IM) routes are individualized for each patient as appropriate to reduce perioperative anxiety. Common medications used for premedication include midazolam, dexmedetomidine, and ketamine (Daaboul et al. 2019). Drug and route selection depends upon the anesthesiologist's discretion and understanding of the pharmacokinetics and pharmacodynamics of the selected agent and the possible effects on the patient's cardiopulmonary status. Other avenues to consider to help with preoperative anxiety, specifically in pediatric patients, are parent present induction and child life specialist involvement when and if appropriate.

The anesthetic of choice for patients undergoing a cardiac hybrid procedure for CHD is GETA as previously mentioned. Thus, a close airway examination before induction and/or review of the prior anesthetic record is prudent. Anticipated difficult airways, especially in syndromic patients, require meticulous planning which may involve having the appropriate equipment readily available in the room, such as video laryngoscopes, fiberoptic bronchoscopes, intubating laryngeal mask airways (LMA), and appropriate personnel notified or available, such as otolaryngologist or another anesthesiologist. A smooth and quick airway securement is highly desirable, especially in patients with poor cardiac reserve or dependent on systemic vascular resistance (SVR) and pulmonary vascular resistance (PVR) balance.

Preprocedural Considerations

Depending on the particular planned intervention or the particular intricacies of the case including the patient's clinical and functional status, it might be advantageous to pre-admit the patient to the hospital before the planned intervention for medical optimization. Admission and initiation of lusitropic and/or inotropic agents along with aggressive diuresis if indicated help to facilitate and improve the patient's cardiac function and end-organ perfusion before the planned proce-

dure. In our experience, this "medical optimization" strategy does lead to faster recovery and much better patient outcomes including a smoother anesthetic.

Procedure Considerations

Ideally, a cardiac hybrid procedure for CHD patients takes place in a room that is designed specifically for such a case with special considerations for the multidisciplinary teams involved including cardiothoracic surgery, anesthesiology, interventional cardiology, perfusion, cardiac catheterization staff, and operating room (OR) staff. However, the reality may be that a cardiac catheterization room or less commonly an OR was retrofitted into a hybrid room to accommodate for the case (Brodt 2018). Notable challenges involved in working in the cardiac catheterization laboratory environment include restricted access to patients, poor lighting, limited functional workspace, radiation exposure, offsite location, and difficult direct communication among team members. In addition, ambient temperature regulation is limited which can predispose patients to hypothermia, especially in small young patients (Daaboul et al. 2019). Available countermeasures to consider include an active warming blanket, endotracheal tube humidifier, thermal cap for neonates and infants, and heating lamps.

Specific procedural considerations for working in a combined surgical and cardiac catheterization laboratory must be anticipated. A strict OR sterile environment must be practiced by all personnel. Radiation safety in a cardiac catheterization laboratory must be adhered to by every team member involved. This includes proper radiation shielding, such as appropriately sized lead gowns, thyroid shields, eye shields, and mobile shields. One should maximize the physical distance from the radiation source whenever possible. It is recommended to wear dosimeters to monitor cumulative radiation exposure when working in an environment with radiation (Lam et al. 2015).

Unlike the operating room, access to the patient in the cardiac catheterization laboratory is more limited as mentioned. Thus, there are anesthetic-specific considerations when working in such a hybrid environment. The anesthetic circuit must be expandable, drip and IV lines must be extended, and monitor cables must be long enough to reach the patient. Radiolucent EKG stickers and leads are preferred to avoid obstruction on fluoroscopy. In addition, radiolucent defibrillator pads are required for the same reason.

Patient positioning is limited and distinct in a cardiac catheterization laboratory compared to the OR. The procedure bed range of motion is restricted as compared to the OR bed. Additionally, the cardiologist controls the bed movement rather than the anesthesiologist in this setting since the bed control is at the foot of the bed. The patient's arms are positioned up and away from the chest rather than at the sides due to fluoroscopic imaging obstruction if a lateral imaging camera is being utilized. So, care must be taken to position and pad the arms to avoid stretch and pressure injury to the brachial plexuses (Daaboul et al. 2019).

Working in a cardiac hybrid environment has many unique challenges for the multidisciplinary teams involved that require significant preoperative planning and open discussion. Effective communication, collaborative teamwork, and mutual respect for each team's expertise are vital when working in such a dynamic high-risk environment. A team huddle to discuss procedure risks, surgical access or approach, interventional procedure, and back-up mechanical circulatory support is essential (Odegard et al. 2016a, b). Surgical access for hybrid procedures includes vascular cutdown for sheath cannulation or sternotomy for direct central cannulation or transapical cannulation. The interventional procedure includes stents, valve, or occlusion device implantation. Back-up mechanical circulatory support includes extracorporeal membrane oxygenation (ECMO) or cardiopulmonary bypass (CPB).

Intraoperative Management

Induction

The decision for mask or IV induction in pediatric patients depends on the patient's hemodynamic stability, cardiac lesion, anticipated hemodynamic effects of induction agents, and available IV access. It is always ideal to have preoperative IV access for IV induction. However, it is not always the case in pediatric patients that preoperative IV access is present or easily obtained. Mask induction with sevoflurane or IM induction with ketamine may be viable alternatives for some patients. Common IV induction agents include fast-acting narcotics, propofol, ketamine, or etomidate. Agent selection and dosing depend on a thorough understanding of the selected agent and its effect on hemodynamics. Titration of the anesthetic agent is key as opposed to the specific agent itself. It is necessary to be prepared, anticipate, prevent, and communicate to avoid life-threatening scenarios (Daaboul et al. 2019).

Monitors

Hemodynamic goals for each patient depend on the underlying CHD lesion. It is helpful to categorize the goals in terms of preload, contractility, afterload, heart rate, and rhythm. Deviations from the goals should be anticipated and corrected promptly to prevent decompensation. Standard ASA monitors which include five lead EKG, noninvasive blood pressure, pulse oximetry, end-tidal carbon dioxide, and temperature are routine monitoring requirements for all GETA cases. In addition, invasive arterial monitor and central venous access for close hemodynamic monitoring and resuscitation are indicated in these cases (Daaboul et al. 2019). It is important to discuss with the surgical and cardiology teams with regard to planned surgical access for the procedure before placement of invasive arterial and venous access to avoid interference. For instance, if a carotid cutdown is planned, then central venous access is best avoided on the same side of the neck. Other intraoperative monitoring to consider includes cerebral oximetry and transesophageal echocardiography (TEE). It is an uncommon practice to place Swan-Ganz catheter for these cases, especially in young pediatric patients.

Medications

If mask induction is performed, then IM succinylcholine and atropine must be available for possible laryngospasm before securing IV access. Bolus vasoactive medications diluted to appropriate concentrations should be readily available to maintain hemodynamic goals. Vasoactive drips such as epinephrine, milrinone, and vasopressin should also be readily available or infusing as indicated. Special considerations include dextrose-containing solution for neonates to maintain appropriate glucose levels, prostaglandin E2 (PGE2) for ductal dependent patients, and inhale nitric oxide (iNO) for patients with pulmonary hypertension.

Anesthetic Maintenance

Maintenance of anesthesia consists of volatile anesthetic, total intravenous anesthesia (TIVA), or a combination of the two techniques. It is common practice to keep the patients paralyzed during the case and maintain them on a combination of low dose volatile anesthetic with supplemental IV sedation as tolerated by the patient. Commonly used sedation drips include short-acting narcotics such as fentanyl or dexmedetomidine. Propofol or ketamine drips can be considered as well.

Special Considerations

Acute and significant hemorrhage can occur with surgical access. So, close attention to the surgical access site must be maintained at all times. Blood products must be available in the room and

checked before incision. Arrhythmias are common with wire manipulations or electrocautery use during sternotomy. Sustained and unstable arrhythmias must be cardioverted or defibrillated as necessary. Temporary pacing via transcutaneous pads may be needed for iatrogenic heart block.

Anticoagulation with heparin bolus is needed to prevent clot formation on the access sheath and wires leading to thromboembolic events. Thus, baseline activated clotting time (ACT) should be checked and rechecked at intervals after the initial heparin dose is given to maintain appropriate levels around 180–220 s, which is adequate for ECMO if needed. Common initial heparin dosing in the cardiac catheterization laboratory is 50 U/kg as compared to 300 U/kg in a CPB case, which requires an ACT greater than 400 seconds. Redosing of heparin may be needed depending on the length of the procedure.

Upon completion of the procedure, heparin is reversed with protamine unless the patient requires postoperative ECMO. The surgical site is decannulated by the surgeon. Adequate hemostasis must be obtained before surgical closure. The patient's coagulation status can be assessed with ACT or heparin concentration to make sure heparin is adequately reversed, coagulation panel, platelet count, rotational thromboelastometry (ROTEM), or thromboelastography (TEG). Blood components, such as platelets, fresh frozen plasma, or cryoprecipitate, can be given as indicated to correct abnormal laboratory test values and evidence of surgical oozing. The use of fibrinogen concentrate, prothrombin complex concentrate, or other factor concentrates such as factor VII could be considered if indicated but may not be available at some institutions.

The decision to extubate the patient after the procedure should be discussed among surgery, cardiology, and anesthesiology teams. If the patient is hemodynamically stable and hemostasis is adequate, then it is reasonable to reverse paralytic as necessary, emerge the patient, and extubate. However, if the patient is labile or anticipated to be labile perioperatively, then it is safest to keep the patient intubated.

Postoperative Considerations

The disposition of patients who undergo a hybrid procedure for CHD should be in the cardiothoracic intensive care unit (ICU) regardless of whether the patient is extubated or not. A step-down unit or ward may be less equipped to manage fresh postoperative complications from both a resource and staffing perspective. Postoperatively these patients still require close monitoring for cardiopulmonary stability, bleeding status, and device stability.

The transition of patient care to the ICU team needs to be systematic and thorough at the bedside. Reports from surgical, cardiology, and anesthesiology teams must be given to the ICU team who will be taking over the next phase of care for the patient. Surgical access, the procedure performed, airway status, vascular access, blood products given, drips status, and any intraoperative complications or findings should be discussed.

Summary

Medicine and technology continue to evolve with time. Hybrid cardiac procedures for CHD are relatively new and innovative in development but will soon be routine. The spectrum of what is possible when it comes to cardiac procedures for patients with CHD will continue to advance and expand. So, be ready to face the challenges and overcome the obstacles as a multispecialty team working together to provide new hope and opportunities to CHD patients.

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Transcatheter Interventional Techniques in the Adult Congenital Heart Disease Patient

Weiyi Tan and Jamil Aboulhosn

Introduction

Cardiac catheterization procedures have altered and revolutionized the treatment of patients with congenital heart disease. The first cardiac catheterization was performed on himself by Dr. Werner Forssmann in 1929 (Meyer 1990). Percutaneous interventions to treat congenital cardiac conditions started with pulmonary valvuloplasty and static balloon atrial septostomy in the 1950s and 1960s (Rashkind and Miller 1966), and the first atrial septal defect (ASD) closure was described by King and Mills in 1976 (King et al. 1976). Since then, there has been exponential growth in both the type and number of transcatheter interventions in patients with congenital heart disease.

Due to advances in medical, surgical, and interventional therapies, patients with congenital heart disease are now living well into adulthood. These adult patients often require a number of interventions throughout their lifetime, to either treat residual cardiac issues or sequelae from their initial surgical repair or palliation (Lui et al. 2017; Stout et al. 2019).

With improvements in medical technology and device design, patients who previously would have required cardiac surgery are now treated with catheter-based procedures. This chapter aims to highlight the currently available transcatheter interventional procedures for adults with congenital heart disease, as well as the indications for their use, potential risks/complications, special considerations, and clinical outcomes for each intervention so that the reader may better understand the procedures and improve the periprocedural management of these patients.

Shunt-Related Interventions

Atrial-Level Shunts

Ostium Secundum ASD Closure

Ostium secundum type atrial septal defect (ASD) is the most common congenital heart malformation encountered in adults, accounting for about 10–15% (Van Der Linde et al. 2011; Marelli et al. 2014). Adult patients often present with symptoms of progressive dyspnea on exertion, palpitations, and decreased exercise tolerance as a consequence of chronic left to right shunting leading to right heart enlargement

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from volume overload, right ventricular dysfunction, progressive tricuspid regurgitation, atrial arrhythmias, and progressive pulmonary hypertension (Rostad and Sörland 1979). Patients who are asymptomatic early in life may develop symptoms as the degree of left-to-right shunting increases with age due to decreased left atrial and ventricular compliance, as well as increased systemic arterial resistance. ASD closure should be considered in symptomatic patients; or in asymptomatic patients with the presence of moderate or greater degree of left to right shunting, as defined by a Q_p:Q_s > 1.5:1 and evidenced non-invasively by the presence of right heart enlargement. The presence of severely elevated pulmonary arterial resistance is considered a contraindication to ASD closure; ideally ASD closure should be considered in those with significant left to right shunting in the presence of normal or low pulmonary vascular resistance (less than 1/3 of the systemic vascular resistance) (Stout et al. 2019). Although patients with severe pulmonary hypertension are usually not candidates for ASD closure, the use of pulmonary vasodilator therapy may reduce the pulmonary arterial pressure and resistance enough to permit ASD closure, with or without the use of a fenestrated device. However, such an approach is not considered to be standard of care and medical treatment of severe pulmonary hypertension without ASD closure is favored (Bradley et al. 2019; Yan et al. 2020). Surgical closure used to be the standard of care for all atrial septal defects (see Fig. 1), and still is for very large ASDs and/or those with deficient posterior and inferior rims, but over the past few decades transcatheter closure of ostium secundum atrial septal defects has largely supplanted surgery as the technique of choice (Singh et al. 2015; Du et al. 2002).

The technique for transcatheter closure of an ostium secundum ASD varies depending on the type of device used, but the principles are the same. The procedure is performed under fluoroscopy and imaging guidance with either transesophageal echocardiography (TEE) or intracardiac echocardiography (ICE). Patients are usually under deep sedation or general anesthesia for TEE procedures and can be under moderate sedation for procedures utilizing ICE. Accurate sizing of the ASD, determination of adequate

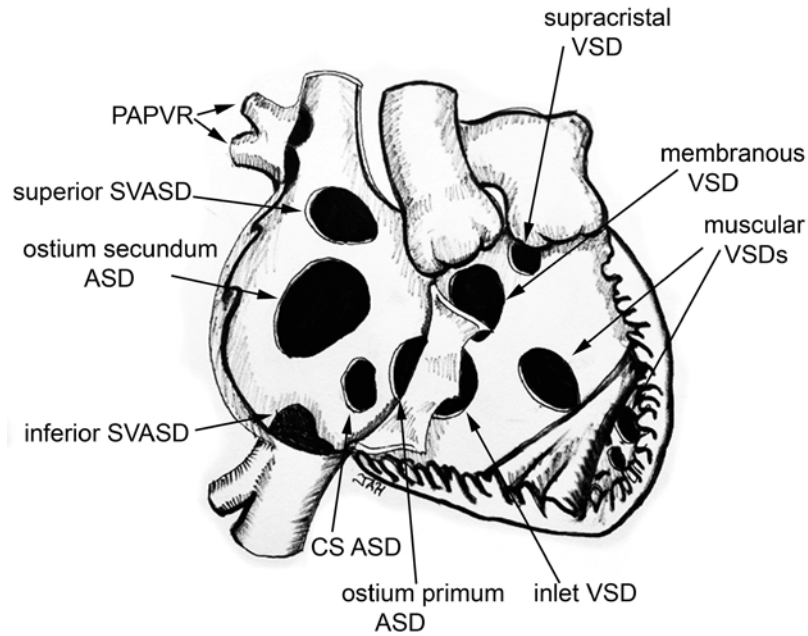

Fig. 1 Different types of atrial septal defects

rims, and the exclusion of associated cardiac anomalies are the cornerstones to successful percutaneous closure of an ASD (Silvestry et al. 2009, 2015). Transesophageal echocardiography is often used to screen defects for closure and to rule out partial anomalous pulmonary venous connections (Silvestry et al. 2009; Hascoët et al. 2016). Intracardiac echocardiography (ICE) has also been described as a method for both selection of septal occluder size and for guidance during transcatheter closure (Rigatelli 2005; Basman et al. 2017).

Delivery sheath insertion is typically via the femoral vein. Despite the availability of a number of closure devices, the procedural success rates are high (complete closure with stable positioning of the device), in the 94–98% range (Sommer et al. 2020; Turner et al. 2017). The first Food and Drug Administration (FDA) approved and still the most commonly used device in the United States is the time-tested and reliable Amplatzer septal occluder (Abbott Laboratories, Abbott Park, IL) (Fig. 2) (Turner et al. 2017; Masura et al. 2005). Of the 1000 patients enrolled in a post-approval study, the Amplatzer device caused complications in only 0.65% ($n = 6$) patients, with a cardiac erosion risk of 0.3% over 2 years (Turner et al. 2017). The Amplatzer multi-fenestrated septal occluder is a variant designed for the treatment of multi-fenestrated defects that are close together and allow for one device to cover multiple holes. The Gore Cardioform ASD occluder (Gore Medical, Flagstaff, AZ) as well as the Gore Cardioform Septal Occluder can be used for closure of ostium secundum ASDs (Fig. 3). The Gore Cardioform Septal occluder comes in sizes ranging from 20 to 30 mm and the Gore Cardioform ASD occluder has sizes ranging from 27 to 48 mm. The devices are approved by the FDA and have excellent short-term results (Sommer et al. 2020). There was a serious adverse event rate of 4.8% ($n = 6$) in the study that led to FDA approval for the ASD

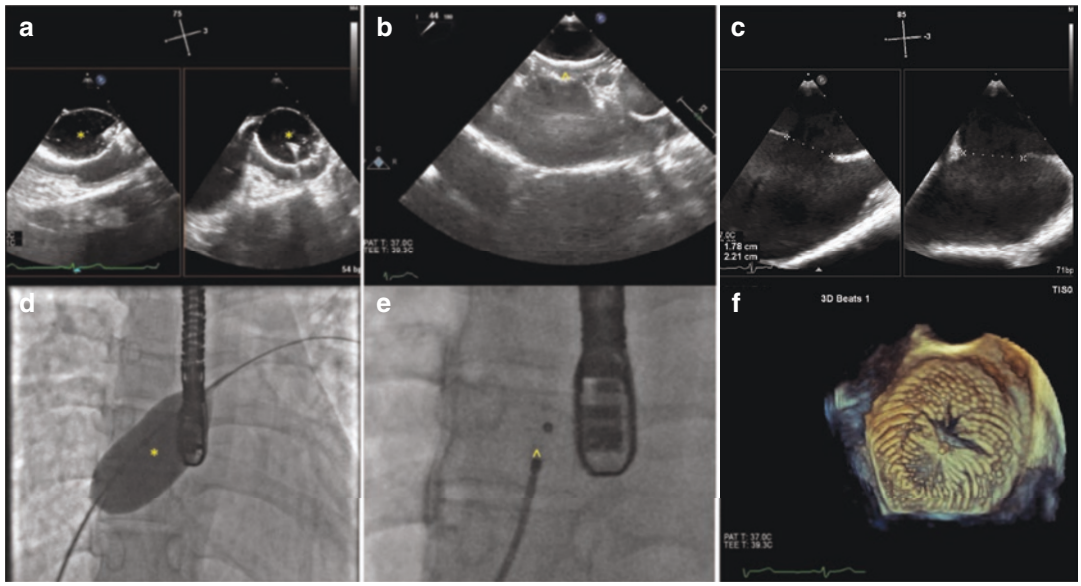

Fig. 2 Closure of an Atrial Septal Defect with an Amplatzer Septal Occluder. (**a**, **d**) Balloon sizing of the atrial septal defect. The top pane (**a**) is an X-plane of the atrial septal defect with transesophageal echocardiography (TEE) imaging during balloon occlusion of the defect with a sizing balloon. The bottom pane (**d**) is a fluoroscopic image of the sizing balloon across the atrial septal defect. There is a slight waist. (**b**, **e**) Deployment of the Amplatzer Septal Occluder. The top pane (**b**) is a TEE image of the device deployed across the atrial septum, and it appears well seated and splayed around the aorta. The bottom pane (**e**) is a fluoroscopic image of the device. (**c**, **f**) Before and after. The top pane (**c**) is a TEE image of the atrial septal defect before closure, measuring 18 × 22 mm in diameter. The bottom pane (**f**) is a 3-dimensional TE×E image of the Amplatzer septal occluder in its final position across the defect. * = sizing balloon, ^ = Amplatzer Septal Occluder

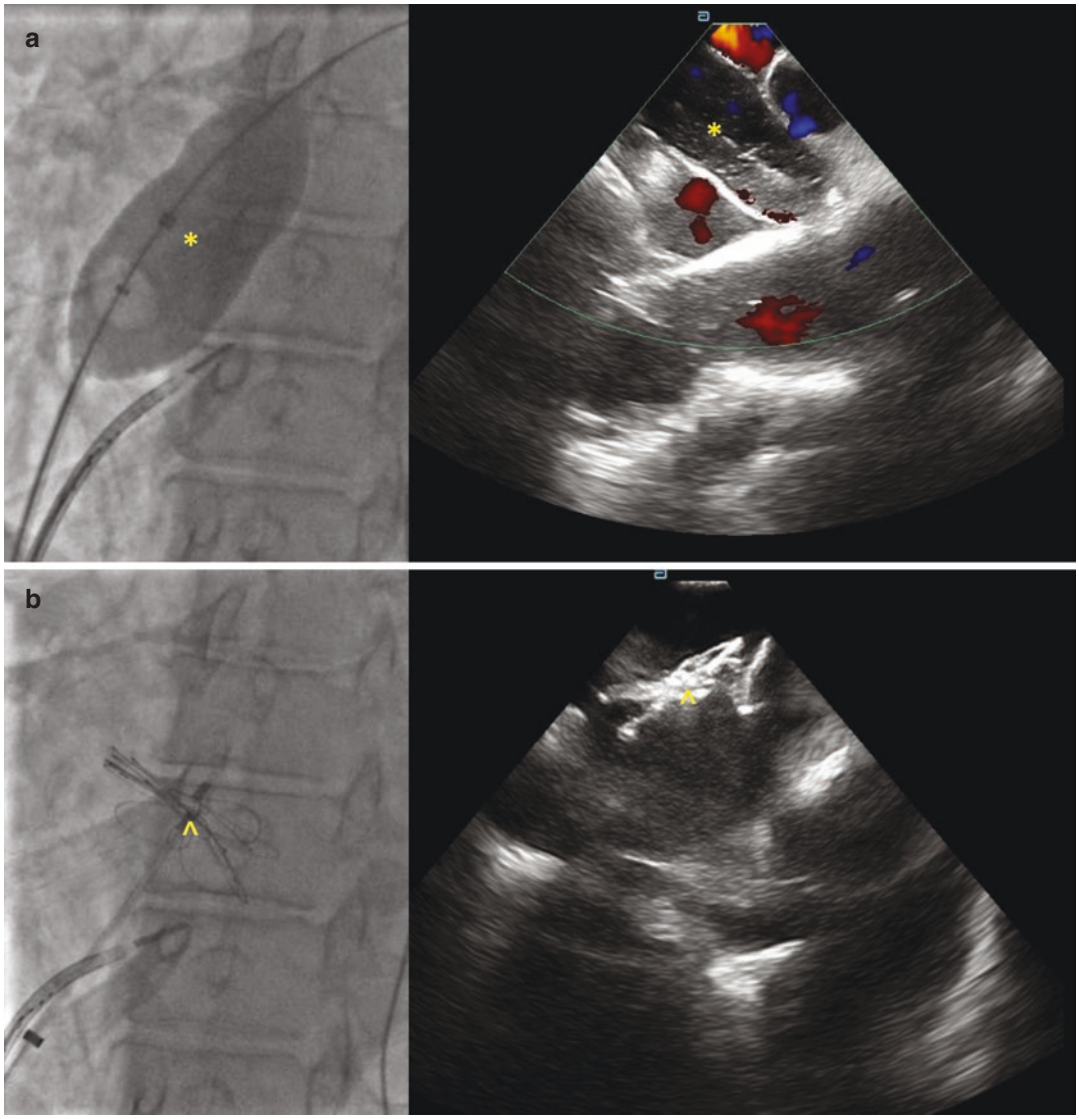

Fig. 3 Closure of an Atrial Septal Defect (ASD) with a Gore Cardioform ASD Occluder. (**a**) Balloon sizing the atrial septal defect (ASD). The left pane is a fluoroscopic image of the sizing balloon across the ASD. Note the small waist. The right pane is an intracardiac echo (ICE) image of the sizing balloon across the defect, with no evidence of Doppler color flow around the balloon. (**b**) Closure of the ASD with a Gore Cardioform ASD occluder. The left pane is a fluoroscopic image of the Gore Cardioform ASD device deployed across the atrial septal defect. The right pane is an ICE image of the deployed device, which is well seated across the atrial septal defect. * = sizing balloon, ^ = Gore Cardioform ASD occluder

occluder, mostly for transient arrhythmias and two episodes of device embolization. The rate of wire frame fracture was surprisingly high, with an event rate of 36% ($n = 37$), but there was no effect with regard to clinical sequelae, residual shunt, or device instability (Sommer et al. 2020). Nevertheless, all devices carry a rare short-term risk of embolization, thrombus formation, aortic root perforation/erosion (Kumar et al. 2020; Amin et al. 2004), pericardial effusion, and arrhythmias, and thus clinical and echocardiographic monitoring over time are warranted.

In older patients, presence of left atrial and/or left ventricular diastolic dysfunction in the setting

of chronic left to right shunting and an underfilled left ventricle may result in increased left atrial and left ventricular filling pressures post device closure of ASD due to redirection of all left atrial volume to the left ventricle. Therefore, careful hemodynamic assessment (this requires a second venous access) of the left atrial pressure pre-closure and during temporary balloon occlusion of the atrial septal defect is of paramount importance in such patients. The use of fenestrated ASD devices may help in such patients (Abdelkarim et al. 2016). Device erosion is a rare but dreaded complication that has been reported with various devices, most commonly the Amplatzer septal occluder, especially when oversizing occurs with larger devices and in those with deficient anterior-superior rims (McElhinney et al. 2016a).

Patent Foramen Ovale Closure

Patent foramen ovale (PFO) is a common anatomic variant that is a residual consequence of fetal circulation. The prevalence of a PFO is estimated to be around 25% of the general population (Kent et al. 2013). Closure of a PFO is indicated when it leads to symptoms, such as platypnea-orthodeoxia (Blanche et al. 2013), persistent hypoxia due to tricuspid regurgitation shunting blood across the PFO (Zuberi et al. 2015), or in the case of a cryptogenic stroke (Saver et al. 2017; Mas et al. 2017; Søndergaard et al. 2017). In the case of cryptogenic stroke, once the PFO is deemed to be the major contributing factor (as evidenced by the RoPE score) (Kent et al. 2013), then patients may be candidates for PFO closure. The technique for PFO closure is similar to that of ASD closure (Rigatelli et al. 2016).

Currently there are two devices, the Amplatzer PFO occluder and the Gore Cardioform Septal Occluder, that are FDA approved for PFO closure in the United States. While these devices have excellent procedural outcomes (Saver et al. 2017; Mas et al. 2017; Søndergaard et al. 2017) and help reduce the absolute stroke risk by 3.3% in one meta-analysis (Shah et al. 2018), leading to a number needed to treat of 30, there is an increased risk of new-onset atrial fibrillation of about 3.4% in one meta-analysis (De Rosa et al. 2018). Other complications, such as pericardial effusion (Kumar et al. 2020), device embolization, and device erosion, are extremely rare.

Superior Sinus Venosus Defect Stenting

Sinus venosus defects are rare, comprising about 5–10% of all atrial septal defects (Attenhofer Jost et al. 2005). There are two types, a superior and inferior sinus venosus defect. The superior sinus venosus defect (SVASD) is a deficiency of the common wall between the superior vena cava (SVC) and right-sided pulmonary veins and is associated with an anomalous right upper pulmonary vein in up to 90% of cases. The inferior SVASD is a deficiency of the wall between the right atrium/inferior vena cava (RA/IVC) and the left atrium, and can be associated with anomalous pulmonary venous drainage of the right lower pulmonary veins to the IVC or RA (Li et al. 1998). Patients with sinus venosus defects usually present with symptoms similar to patients with an ostium secundum ASD, although they may present earlier due to increased left-to-right shunting from both an atrial-level shunt and from one or more anomalous right-sided pulmonary veins that drain into the superior vena cava (SVC). Once these patients are diagnosed with a sinus venosus defect, almost all are referred for surgical or transcatheter correction of this defect due to the large left-to-right shunt from both the atrial-level defect and the anomalous pulmonary veins that leads to right heart enlargement and symptoms of dyspnea on exertion, decreased exercise tolerance, or even right-heart failure (Riahi et al. 2018). The 2018 ACC/AHA (American College of Cardiology/American Heart Association) guidelines still recommend surgical closure of these defects (Stout et al. 2019) and many of these patients will do well with surgery. Surgical correction with the Warden procedure or two-patch repair, however, still leads to complications like recurrent pulmonary vein stenosis, SVC stenosis, or sinus node dysfunction (Attenhofer Jost et al. 2005; Stewart et al. 2007). Over the past decade, transcatheter correction of superior sinus venosus defects using covered stents has become more estab-

lished (Riahi et al. 2018; Thakkar et al. 2018; Garg et al. 2014; Abdullah et al. 2020; Hansen et al. 2020).

The procedure is technically challenging and requires significant pre-procedural planning to identify appropriate patients. A preoperative computed tomography angiography of the chest is usually performed to create a virtual or three-dimensional (3D) printed model to help with visualization of the sinus venosus defect, the anomalous pulmonary vein, and the surrounding structures (Thakkar et al. 2018). If the anatomy is favorable for the placement of a covered stent that will direct SVC blood to the right atrium, allowing for unobstructed anomalous pulmonary vein flow to then drain into the left atrium via the residual sinus venosus defect, the patient is then brought to the cardiac catheterization laboratory. The procedure is usually performed under general anesthesia given the need for intraprocedural imaging guidance with TEE.

A description of the largest cohort to date demonstrated that the procedure has good short-term outcomes with no incidence of sinus node dysfunction (Hansen et al. 2020) (Fig. 4). One of the drawbacks of this procedure, however, is the difficulty in using just one stent to adequately cover the SVC superiorly and the SVC-RA junction inferiorly, while maintaining stent stability. Forty percent (n = 10) of the patients in the study required covered CP stents (B. Braun Inc., Irvine, CA) longer than 6 cm, which is currently not available commercially in the United States. Furthermore, 52% (n = 13) of the patients in the study required additional stents to secure the covered stent and 24% of patients (n = 6) had covered stents that either migrated or embolized during the procedure. If the stent is not long enough, there may still be a residual shunt at the inferior margin of the stent, as noted in 44% (n = 11) of the patients in the study by Hansen et al. (2020). In fact, the last 9 patients in the study had custom-made 7 or 8-cm long covered 10-zig CP stents to increase the zone of apposition in the SVC to prevent migration/embolization and to reduce the chance of residual leak

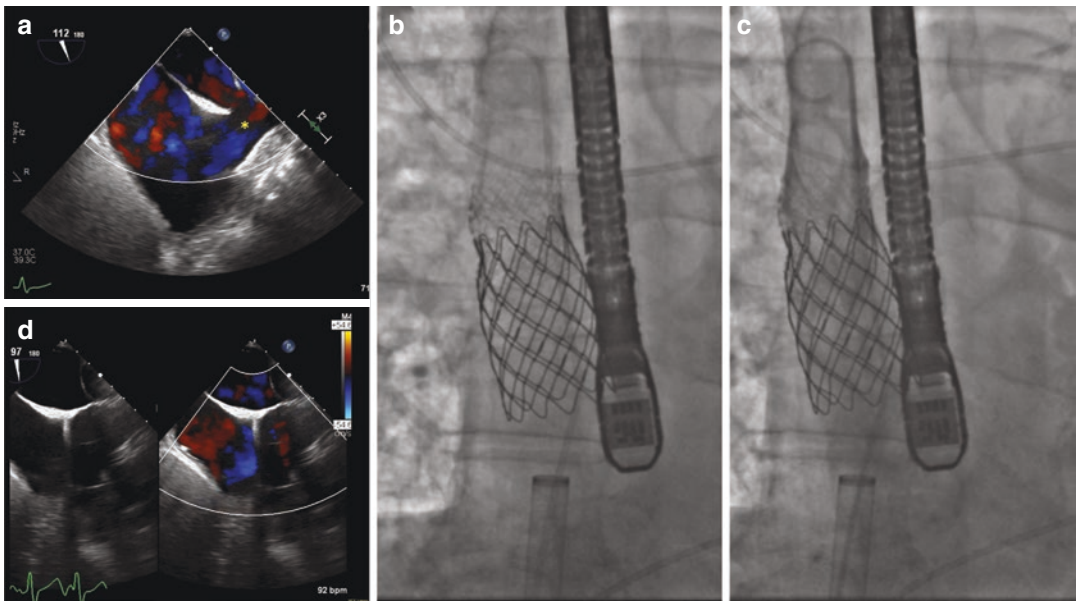

Fig. 4 Superior Sinus Venosus Defect Stenting. (**a**, **d**) The top pane (**a**) is a transesophageal echocardiography (TEE) image of the superior sinus venosus defect (SVASD). There is evidence of low velocity color flow from the left atrium to the right atrium. The bottom pane (**d**) is a TEE image of the covered stent across the defect, allowing blood from the superior vena cava (SVC) to drain into the right atrium (RA) while sealing the SVASD. (**b**) A fluoroscopic image of the covered stent across the SVASD. (**c**) Angiography of the SVC demonstrating flow from the SVC to the RA without any leakage into the left atrium. * = superior sinus venosus defect

around the stent at the SVC-RA junction. Larger studies and more experience with this technique will lead to further iterations and improvements of the procedure, but a select subset of patients with superior sinus venous defects may benefit from transcatheter correction of the defect and avoid a surgical option.

Ventricular Septal Defect Closure

Ventricular septal defects (VSDs) are the most common congenital heart defect in infancy and comprise about 20% of all congenital heart lesions (Morray 2021; Hoffman and Kaplan 2002), and may occur within the muscular or membranous septum (Fig. 5). Patients are usually asymptomatic if the shunt is restrictive; however, a minority of patients may develop signs and symptoms of left heart volume overload later in life (pulmonary venous congestion, shortness of breath, dyspnea on exertion). Adult patients with non-restrictive VSDs are often cyanotic due to supra-systemic levels of pulmonary arterial resistance leading to right-to-left shunting, a condition named the Eisenmenger syndrome (Stout et al. 2019; Diller et al. 2013). The indication for repair of a VSD is evidence of left ventricular volume overload and a hemodynamically significant shunt with a Q_p:Q_s ratio of $\geq$1.5:1, as long as pulmonary pressure or pulmonary vascular resistance is not elevated (Stout et al. 2019). Other indications for VSD closure include progressive aortic valve regurgitation or a history of infective endocarditis. Patients with the Eisenmenger syndrome should not undergo VSD closure but should be treated with pulmonary hypertension medications (Stout et al. 2019).

Transcatheter closure of a VSD can be challenging depending on size and location. These challenges include the variable thickness of the ventricular septum, the variable location of a VSD, the high pressures in the ventricles that can lead to device embolization, the close proximity of the aortic valve to the membranous septum, and the location of the conduction tissue relative to the membranous septum. VSD closure devices must avoid interference with valve function and the conduction system; additionally, ventricular arrhythmias may occur and residual shunting may result in hemolysis (Morray 2021).

The types of VSDs that are amenable to transcatheter closure are usually the membranous and muscular/apical type VSDs (Morray 2021; Butera et al. 2007; Holzer et al. 2006). Inlet type VSDs usually require surgical repair. The procedure is usually performed under general anesthesia as TEE imaging is usually employed for procedural guidance. Closure of the VSD can either be antegrade (requiring the formation of an arteriovenous loop) or retrograde (Fig. 6). The only device that is currently FDA-approved for transcatheter VSD closure is the Amplatzer muscular VSD occluder (Abbott Labs, Abbott Park, IL), and it has been demonstrated to be effective in both congenital and acquired (postmyocardial infarction) muscular VSDs (Holzer et al. 2004a, b). Other devices, such as the ADO I, ADO II, and Amplatzer septal occluder (Abbott Labs, Abbott Park, IL), can be used in an off-label fashion (Morray 2021). Closure of membranous VSDs is feasible, but the development of conduction abnormalities is a major concern, with rates reported as high as 6% of cases (Morray 2021; Butera et al. 2007; Holzer et al. 2006). Closure of membranous ventricular septal defects associated with aneurysms of the ventricular septum is feasible and safe with a low risk of conduction system abnormalities (Pedra et al. 2004). Long-term results are favorable, with procedural success rates in the 90% range and complications such as heart block (up to 6%), hemolysis (1–2%), and embolization (1–2%) being relatively uncommon (Morray 2021).

Patent Ductus Arteriosus Closure

The ductus arteriosus, when patent, is a vestige from fetal circulation that connects the descending aorta and pulmonary artery (Krichenko et al. 1989; Schneider and Moore 2006). There are

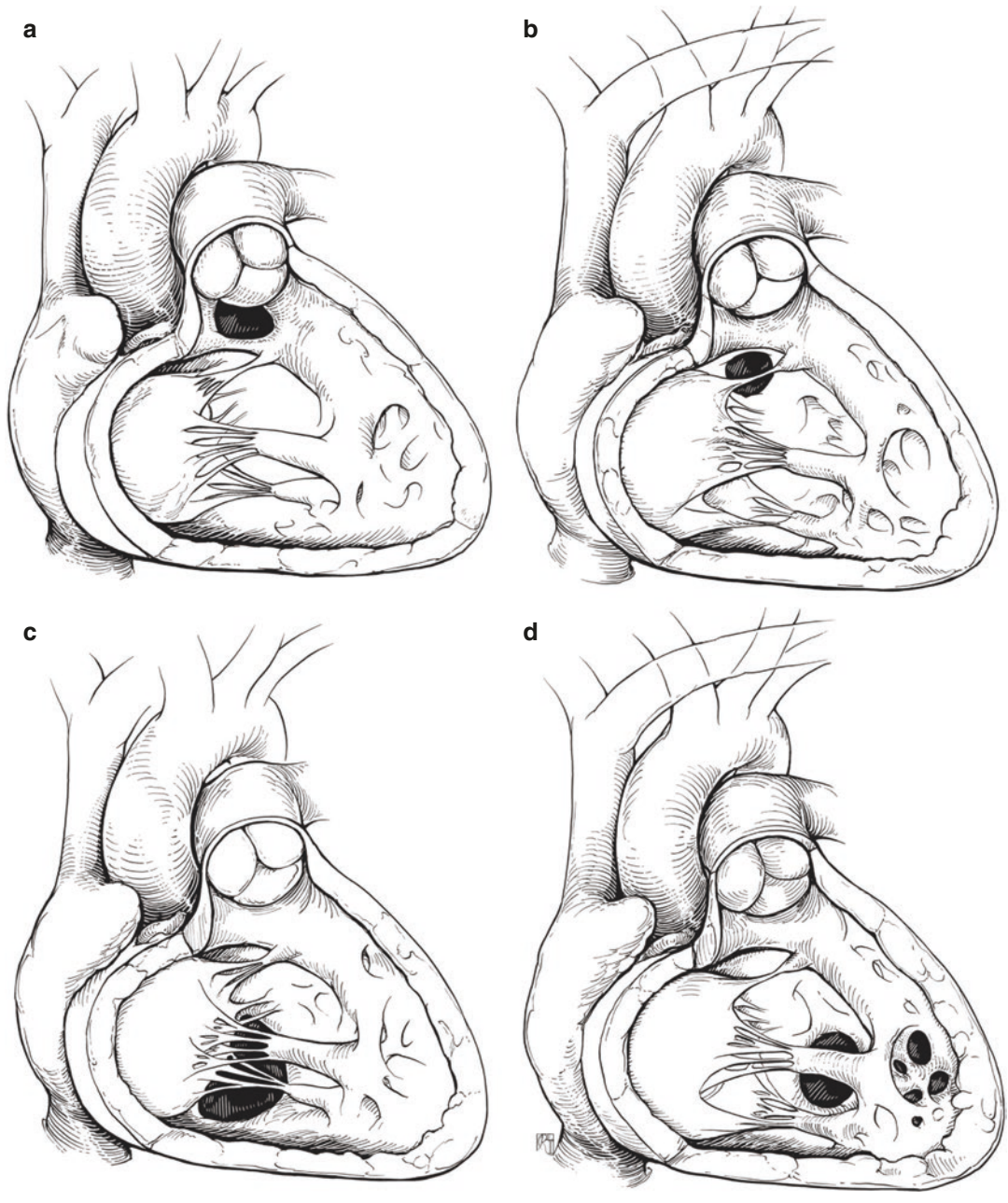

Fig. 5 VSD subtypes https://link.springer.com/chapter/10.1007/978-3-030-14163-9_6#Sec15. Panel **a** shows the so-called type I defect, which is directly adjacent cranially to the leaflets of the tricuspid valve (Supracristal) The type II defect, shown in panel **b**, opens centrally to the right ventricle at the base of the ventricular mass (Perimembranous). The type III defect, shown in panel **c**, is a large defect opening to the inlet of the right ventricle and extending across the full width of the annulus of the tricuspid valve (Inlet). Panel **d** shows several type IV defects, which open apically and are surrounded by the musculature of the ventricular septum (muscular, apical)

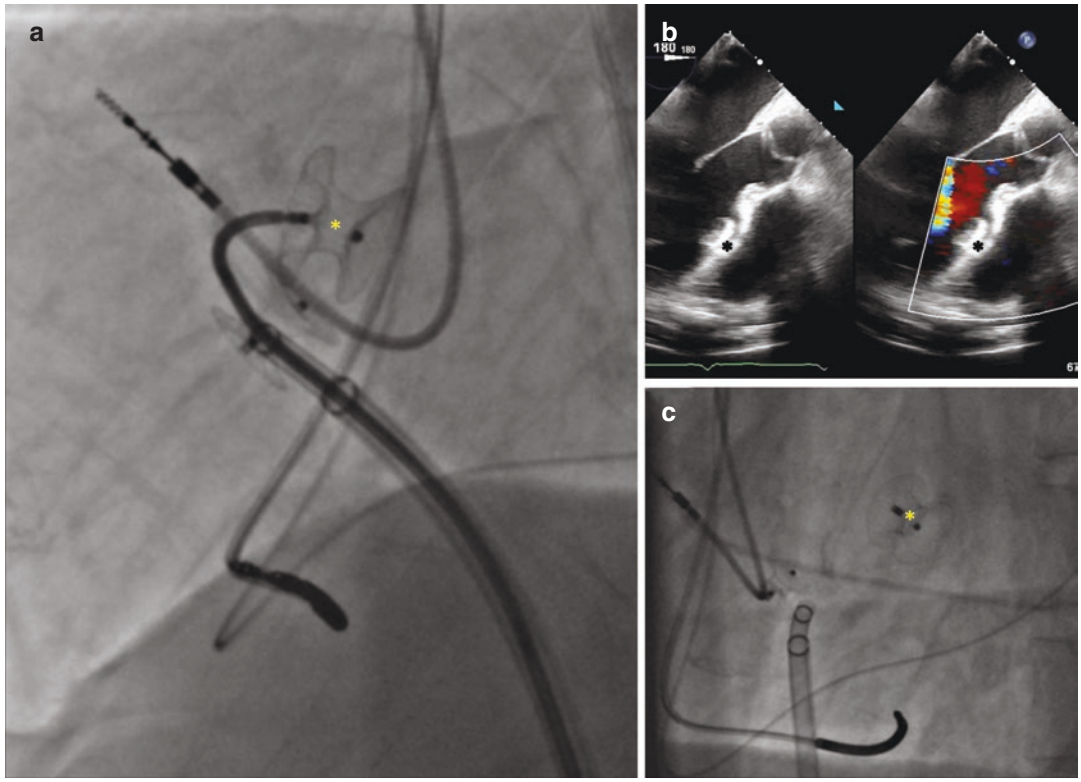

Fig. 6 Transcatheter Ventricular Septal Defect Closure. (**a**) Fluoroscopic image of a muscular ventricular septal defect (VSD) occluder across a muscular VSD. Note a second VSD occluder across a perimembranous defect. (**b**) Transesophageal echocardiographic image of the muscular VSD occluder across the defect, with no evidence of color Doppler flow across the device. (**c**) Final position of the device after releasing the device in a lateral fluoroscopic projection. * = muscular VSD occluder

many morphologies of a patent ductus arteriosus (PDA) (Krichenko et al. 1989; Philip et al. 2016) (Fig. 7). The incidence of an isolated PDA in term infants is about 2.9 per 10,000 live births (Reller et al. 2008), but can also occur in patients with genetic syndromes like DiGeorge syndrome or CHARGE syndrome (Lewis et al. 2018). Adult patients with PDA have variable presentations depending on the size of the PDA. Patients with a small PDA (Q_p:Q_s < 1.5) are often asymptomatic, especially in the first few decades of life, and the diagnosis may be incidental, but most have a continuous murmur on exam. Patients with a moderate-sized PDA (Q_p:Q_s 1.5 to 2.2: 1) may have exercise intolerance, heart failure, and evidence of left-sided (left atrial and/or left ventricular) volume overload as evidenced by chamber enlargement on non-invasive imaging. Adult patients with a large PDA (Q_p:Q_s > 2.2:1) will manifest overt evidence of left heart failure. However, most adults with large PDA who survive the volume overload will eventually develop severe pulmonary hypertension with shunt reversal and differential cyanosis, consistent with the diagnosis of Eisenmenger syndrome.

PDA closure is indicated in patients with left to right shunting who are symptomatic of heart failure or asymptomatic patients with left heart enlargement, in the absence of severe pulmonary hypertension. As is the case for ASD or VSD, PDA closure should not be attempted in those with Eisenmenger syndrome (Stout et al. 2019). Infective endocarditis involving the PDA is not only a rare complication but is also an indication

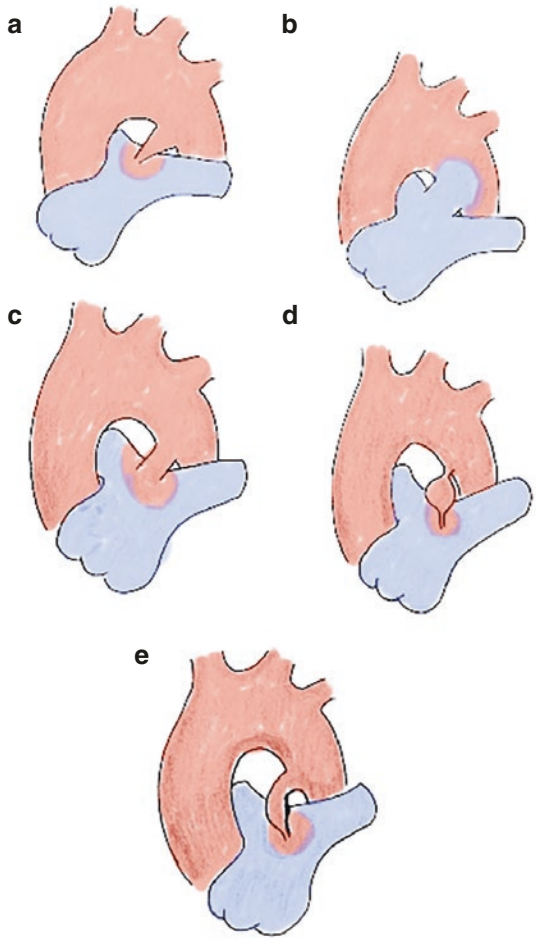

Fig. 7 Subtypes of a Patent Ductus Arteriosus. (**a**) Type A or "Conical" ductus, with a well-defined aortic ampulla and constricted exit at the pulmonary artery. (**b**) Type B or "Window" ductus, with a short length, slightly constricted aortic end and wide pulmonary artery end. (**c**) Type C or "Tubular" ductus, without any constrictions at the aortic end or pulmonary artery end. (**d**) Type D or "Saccular" ductus, with constricted aortic end and pulmonary artery end with a wide center. (**e**) Type E or "Elongated" ductus, which is narrow with a constricted pulmonary artery end. https://onlinelibrary.wiley.com/doi/epdf/10.1002/ccd.26287

for closure when it occurs (Thilen and Astrom-Olsson 1997). In appropriately selected patients, the outcomes of PDA closure are excellent, including in select patients with moderately elevated pulmonary artery pressure and resistance (Pas et al. 2002) (Schneider and Moore 2006). In patients with elevated pulmonary resistance, pulmonary bed vasoreactivity or reduction in pulmonary artery pressure during test occlusion may portend a favorable outcome of transcatheter PDA closure (Schneider and Moore 2006).

The basic technique is to advance a catheter or delivery sheath across the ductus arteriosus from either the pulmonary artery (anterograde) or the aorta (retrograde) and position a closure device in the ductus to occlude it (Schneider and Moore 2006). The armamentarium of potential transcatheter devices includes coils (used for small restrictive defects) and multiple occlusion devices, including the Amplatzer duct occluder (approved in the United States), Occlutech PDA device, and a variety of Chinese Amplatzer like devices not approved in the United States (Schneider and Moore 2006; Pass et al. 2004; Masura et al. 2003; Eicken et al. 2007; Spies et al. 2005) (Moore et al. 2001) (Fig. 8). In certain cases where device closure of the PDA is not feasible, PDA occlusion may be performed with aortic covered stent placement (Sadiq et al. 2003). Patients with PDA and moderately elevated pulmonary arterial resistance (less than 6 Woods Units) can be closed using an Amplatzer Muscular VSD device which has two discs to help anchor the device and thereby reduce risk of device embolization (Eicken et al. 2007). The risks of PDA closure are related to device embolization, obstruction of flow of the branch pulmonary arteries or descending aorta from a protruding device, hemolytic anemia from high-pressure residual shunting across the PDA, vascular access complications, and infection (Schneider and Moore 2006; Spies et al. 2005). Nevertheless, these complications are rare (Wilson et al. 2020).

Valve Interventions

Balloon Angioplasty of Native Pulmonary Valve Stenosis

Pulmonary valve stenosis represents 7% of all congenital heart defects (Stephensen et al. 2004). Pulmonic stenosis may occur at multiple levels in the right ventricular outflow tract/pulmonary artery: valvular, subvalvular, or supravalvular.

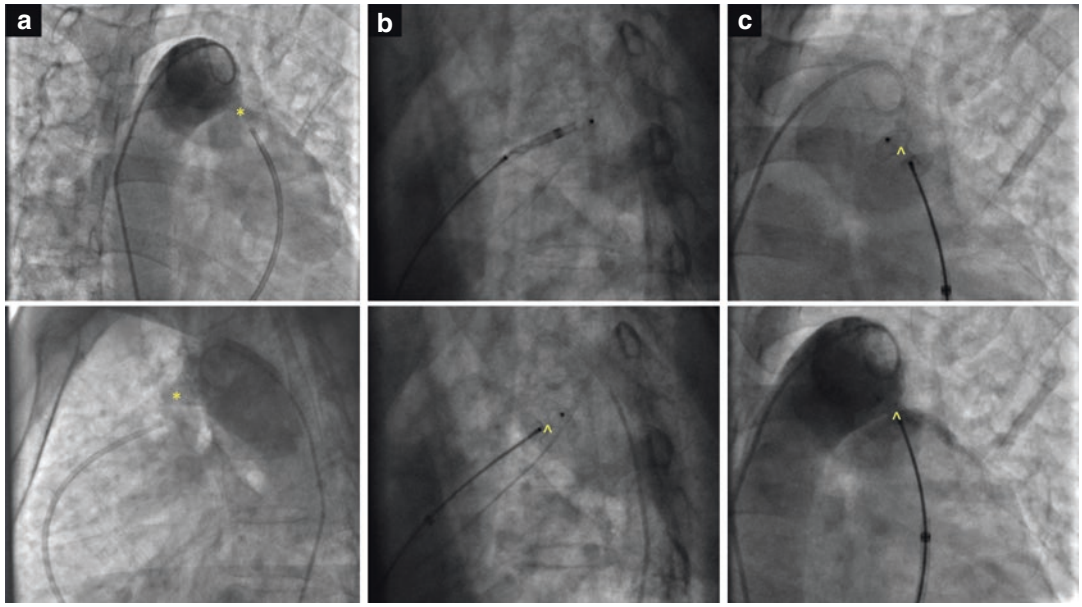

Fig. 8 Transcatheter Closure of a Patent Ductus Arteriosus Transcatheter Pulmonary Valve Replacement with an Edwards Sapien S3 Valve. (**a**) Biplane fluoroscopic image of an angiogram of a patent ductus arteriosus (PDA) with a pigtail catheter in the aorta. There is a wedge catheter in the pulmonary artery. The top pane is the anterior-posterior (AP) projection, and the bottom pane is the lateral projection. (**b**) The top pane is a lateral projection of a muscular ventricular septal defect (VSD) occluder being deployed through a delivery sheath across the PDA. The bottom pane is a lateral projection of the device fully deployed across the PDA. (**c**) The top pane is an AP projection of the device and the bottom pane is an angiogram of the PDA with minimal residual shunting across the defect. The device was released without any complications. * = PDA, ^ = muscular VSD occluder

Subvalvular pulmonic stenosis is typically due to fibromuscular hypertrophy and often associated with double-chambered right ventricle (Karczenski 1988); subvalvular stenosis usually requires surgical resection (Fawzy et al. 1990). Supravalvular pulmonic stenosis is amenable to balloon angioplasty or stenting. Valvular pulmonic stenosis may be isolated or occur in combination with other levels of obstruction and can also be associated with other conditions, such as tetralogy of Fallot (TOF), congenital rubella syndrome, and Noonan syndrome.

Dyspnea on exertion is a common presenting symptom and non-invasive imaging typically demonstrates right ventricular hypertrophy. Pulmonary stenosis is considered if there is a systolic velocity of ≥4 m/s at rest, moderate if the peak velocity is 3–4 m/s, and mild if <3 m/s (Stout et al. 2019). Transcatheter intervention is warranted in symptomatic patients with moderate or severe stenosis or in asymptomatic patients with severe stenosis (Stout et al. 2019).

Isolated static balloon valvuloplasty is the treatment of choice for isolated pulmonary valve stenosis if the valve is mobile and doming. However, 15% of patients present with non-doming restricted and dysplastic leaflets which are not as amenable to successful balloon dilation (McCrindle 1994). Balloon valvuloplasty is associated with slightly higher residual stenosis but lower morbidity when compared to surgical valvotomy, additionally there is less resultant regurgitation, and therefore valvuloplasty has become the treatment of choice for isolated pulmonary valve stenosis (Rostad and Sörland 1979; Basman et al. 2017).

The original catheter-based technique was initially described by Rubio and Limon-Lason in 1956 (Rubio and Limon-Lason 1956). The currently employed percutaneous static balloon valvuloplasty technique was first reported by Kan et al. in 1982 (Kan et al. 1982). Outcomes are excellent and risk of complications is low (Stout et al. 2019; McCrindle 1994; Stanger et al. 1990).

The VACA (Valvuloplasty and Angioplasty of Congenital Anomalies) registry investigators gathered follow-up data on 533 patients who underwent balloon pulmonary valvuloplasty (McCrindle 1994). Over 8 years of follow-up, 23% of patients had a suboptimal outcome, as judged by either a residual peak systolic gradient >36 mmHg or the need for further intervention. Predictors of suboptimal outcome included elevated immediate post-procedure gradient (odds ratio, 1.32 per 10 mmHg increase), a lower ratio of balloon to annulus diameter, and a dysplastic valve. Restenosis is rare (Chen et al. 1996; Rao et al. 1998). The approach to valvuloplasty is via the femoral or jugular vein with desired balloon to pulmonary annulus diameter ratio of 1.2–1.25 (Rao 2007). Balloon/annulus ratios exceeding 1.5 risk rupturing the pulmonary valve annulus (Ring et al. 1985). If the pulmonary annulus is too large for dilatation with a single balloon, two balloons can be employed (Butto et al. 1986).

Pulmonary Valve Replacement

Transcatheter pulmonary valve replacement (TCPVR) can be performed in patients with various underlying conditions and anatomical variations, including in native right ventricular outflow tract (RVOT), those with right ventricle to pulmonary artery conduit (RV-PA conduit), or those with dysfunctional pulmonary surgical bioprostheses (Sinha et al. 2019). Patients with repaired tetralogy of Fallot (TOF) represent the majority of subjects requiring TCPVR (Sinha et al. 2019). The most frequent postoperative anatomy encountered in adults with TOF is native RVOT with predominant pulmonary regurgitation, less frequently encountered are conduits or bioprosthetic valves. Homograft conduits, either aortic or pulmonary, have been used extensively since the 1960s. Progressive dysfunction occurs in the majority of homografts and most require replacement within 15 years from implantation, sooner if implanted in a young child (Kaza et al. 2009). The average time to surgically placed bioprosthetic valve dysfunction is approximately 15 years (Egbe et al. 2019; Lee et al. 2011).

In patients with predominant pulmonary valve regurgitation, the 2018 ACC/AHA guidelines on the management of patients with ACHD recommend consideration of valve replacement in symptomatic (dyspnea, chest pain, and/or exercise intolerance referable to pulmonary valve regurgitation or otherwise unexplained) patients or in asymptomatic patients with evidence of RV or LV systolic dysfunction, severe RV enlargement with an indexed RV end-diastolic volume of >160 mL/m^2 or indexed RV end systolic volume >80 mL/m^2, RV systolic pressure >2/3 systemic pressure, or those with an objective progressive reduction in exercise capacity (Stout et al. 2019). In patients with prosthetic or homograft pulmonic stenosis, the guidelines recommend intervention in a fashion similar to patients with native pulmonic stenosis, which is in symptomatic patients with moderate-to-severe pulmonic stenosis, or asymptomatic patients with severe pulmonic stenosis (Stout et al. 2019).

Dysfunctional bioprosthetic valves can usually be replaced with a relatively straightforward balloon expandable valve in valve procedure (Gillespie et al. 2012; Shahanavaz et al. 2020a). Many bioprosthetic valves can be fractured using high pressure balloon inflation to allow for placement of larger TCPVR to avoid residual stenosis due to patient prosthesis mismatch (Shahanavaz et al. 2018). RV-PA conduits, especially calcified homografts, are at risk of dissection and rupture during high pressure balloon dilation; therefore, covered stent platforms are used to reduce the risk of uncontained rupture and extravasation. Patients with native RVOTs (such as patients with tetralogy of Fallot and transannular patch repair) represent an anatomically heterogeneous group with variable RVOT shapes and sizes that necessitate advanced cross-sectional imaging to assess for TCPVR suitability.

In the current era of TCPVR, the most widely used balloon expandable valves are the Melody Valve (Medtronic Inc., Minneapolis, MN) and Edwards Sapien Valve (Edwards Lifesciences, Irvine CA). The Melody valve is a bovine jugular vein cuff and valve sewn onto a platinum iridium stent frame. The valve sizes range from 18 to 22 mm, but the valve functions well at a

greater range of implant diameters (12 to 24 mm). The Edwards Sapien valve is now in its third generation (Sapien S3) and is FDA approved for use in dysfunctional conduits and bioprosthetic valves (COMPASSION S3 Clinical Trial NCT02744677). The Sapien valves range in size from 20 to 29 mm and are often advanced within a large bore Dryseal (Gore Medical, Flagstaff, AZ) sheath to reduce risk of tricuspid valve injury (Fukuda et al. 2020; Kenny et al. 2019; Fig. 9). Both valve platforms are associated with excellent short- and intermediate-term outcomes (Sinha et al. 2019; Kenny et al. 2018; Cheatham et al. 2015).

Short-term complications include tricuspid valve damage, valve embolization, vascular injury, coronary and aortic compression, or delivery system fracture (Shahanavaz et al. 2020a). Long-term complications include progressive valve dysfunction (Egbe et al. 2019), valve fracture (specific to the Melody valve), and infective endocarditis. Melody stent fracture can be mitigated by pre-stenting of conduits or native RVOT. Infective endocarditis is a serious concern which occurs in approximately 10% of patients over 5 years of follow-up. Risk factors for endocarditis include residual pulmonary stenosis, history of endocarditis, and immune compromise (Lluri et al. 2018; McElhinney et al. 2013, 2018; Sadeghi et al. 2019). The treatment of large diameter (>30 mm) native RVOTs is especially challenging given that the largest commercially available balloon expandable TCPVR platforms is the 29 mm Sapien 3. Hybrid surgical plication of the pulmonary artery can be considered via a sternotomy or thoracotomy in order to establish a "landing zone" for TCPVR (Suleiman et al. 2015). The Venus P valve (Venus Medtech, China) and the Harmony valve (Medtronic, Minneapolis, MN), are self-expanding covered hourglass-shaped RVOT reducer platforms with the valve in the central waist; the Harmony valve is FDA approved in the United States (Benson et al. 2020) (Figs. 10 and 11). The Alterra adaptive RVOT reducer (Edwards Lifesciences) is self-expanding, partially covered nitinol stent platform that has an hour-glass shape and serves to create a landing zone for the 29 mm Sapien S3 valve; this pre-stent was FDA approved in December of 2021 (Shahanavaz et al. 2020b).

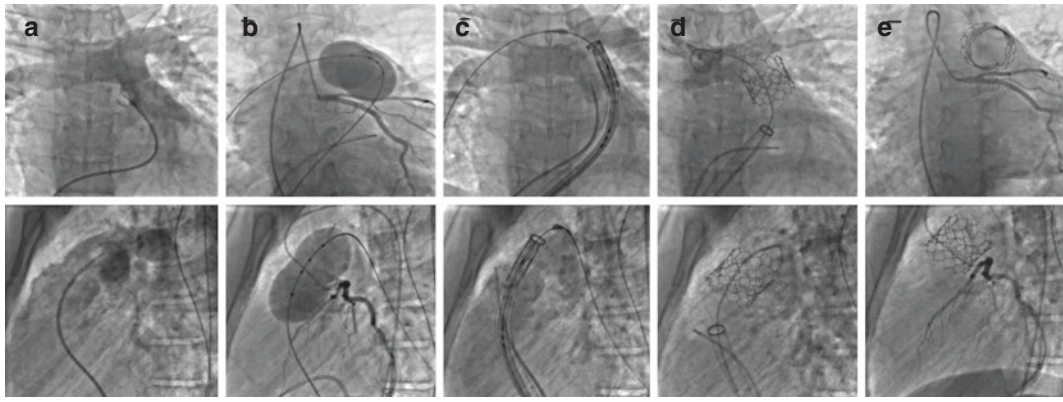

Fig. 9 Transcatheter Pulmonary Valve Replacement with an Edwards Sapien S3 Valve. Each panel is a biplane fluoroscopic image, with the top pane as an anterior-posterior (AP) projection and the bottom pane as a lateral projection. (**a**) Initial angiogram with a Berman angiographic catheter outlining the right ventricular outflow tract (RVOT) and the pulmonary artery, with severe pulmonary regurgitation. (**b**) Coronary compression testing with selective angiography of the left coronary artery and simultaneous balloon inflation across the landing zone for the transcatheter pulmonary valve in the RVOT. There is no coronary compression noted. (**c**) Delivery of the transcatheter pulmonary valve (Edwards Sapien 3, Edwards Lifesciences, Irvine, CA) via a Dryseal sheath. (**d**) Biplane image of the deployed Sapien 3 valve in the pulmonary position, with stable positioning of the valve and normal function of the valve on angiography and intracardiac echocardiography. (**e**) Selective coronary angiography demonstrating no evidence of coronary compression after deployment of the valve

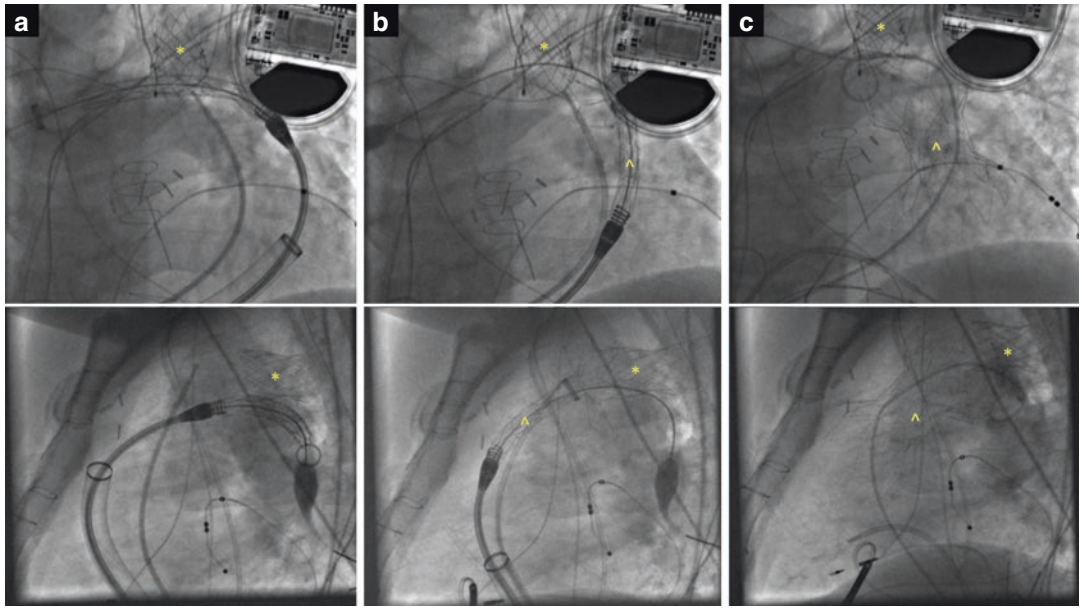

Fig. 10 Harmony Transcatheter Pulmonary Valve Replacement (Fluoroscopic Images). Each panel is a biplane fluoroscopic image, with the top pane representing the anterior-posterior projection and the bottom pane representing the lateral projection. (**a**) Advancing the Harmony valve delivery system through a Dryseal sheath into the right pulmonary artery, while avoiding interaction with the proximal left pulmonary artery (LPA) stent. (**b**) Unsheathing the Harmony valve in the main pulmonary artery, while still avoiding interaction with the LPA stent. (**c**) The Harmony valve is fully deployed and released, with excellent positioning of the valve and no evidence of pulmonary regurgitation on angiography. * = LPA stent, ^ = Harmony Valve

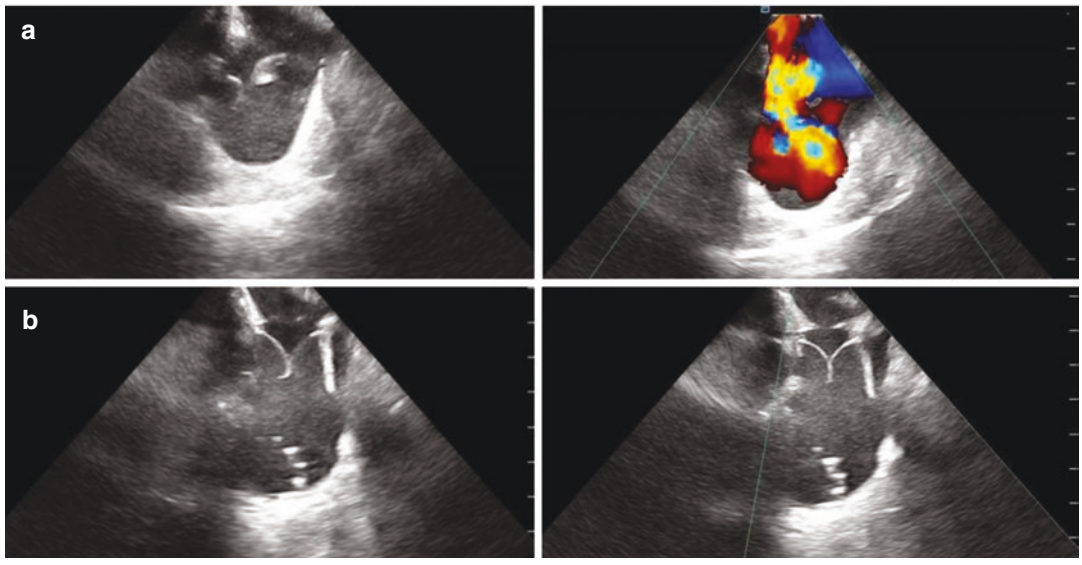

Fig. 11 Harmony Transcatheter Pulmonary Valve Replacement (Intracardiac Echocardiography Images). (**a**) Intracardiac echocardiography (ICE) images before the Harmony valve deployment. The left pane demonstrates remnants of native pulmonary valve tissue. The right pane is a color Doppler of the native valve, demonstrating severe pulmonary valve regurgitation. (**b**) ICE imaging after Harmony valve implantation. The left pane demonstrates the Harmony valve in stable position. The right pane is a color Doppler image of the valve in diastole, demonstrating no evidence of intravalvular or perivalvular leak

Percutaneous Repair of Native Atrioventricular Valve Regurgitation

Atrioventricular valve regurgitation is a common long-term complication of a variety of ACHD conditions. For example, patients with congenitally corrected transposition of the great arteries often develop left atrioventricular valve regurgitation (Franzen et al. 2011). Patients with unbalanced atrioventricular septal defects and single ventricle physiology also develop significant atrioventricular valve regurgitation over time (Buratto et al. 2017). The 2018 ACC/AHA ACHD guidelines (Stout et al. 2019) recommend extrapolation of the ACC/AHA guidelines for the management of valvular heart disease for mitral valve regurgitation, which are to intervene in severe regurgitation in the presence of symptoms (heart failure, dyspnea, decreased exercise tolerance), or in asymptomatic patients with evidence of ventricular dysfunction (Otto et al. 2020).

Surgical treatment of atrioventricular valve regurgitation is considered standard of care for ACHD patients; however, there are occasional cases that are considered to at very high or prohibitive surgical risk where transcatheter options have been successfully utilized (Otto et al. 2020; Feldman et al. 2011; Stone et al. 2018). The use of the Mitraclip (Abbott Laboratories, Chicago, IL) has been established as an effective therapy in adult patients with primary and secondary mitral valve regurgitation (Feldman et al. 2011; Stone et al. 2018). The Mitraclip has been used in select ACHD patients, including in those with transposition complexes and single ventricle physiology (Alshawabkeh et al. 2021; Tan et al. 2020) (See Figs. 12 and 13). Excellent imaging with transesophageal echocardiography is essential (Tan and Aboulhosn 2019). Early feasibility studies of new technologies, such as the Edwards PASCAL system (Edwards Lifesciences, Irvine, CA), also show promising results (Kodali et al. 2021).

Prosthetic Atrioventricular Valve Replacement

Tricuspid Valve

Primary tricuspid valve dysfunction in ACHD patients may be secondary to a variety of etiologies ranging from anatomic valve abnormalities (e.g., Ebstein's anomaly) to functional regurgitation due to right ventricular volume and/or pressure overload (Burri et al. 2016; Ghobrial and Aboulhosn 2018; Jones et al. 2016). Tricuspid valve regurgitation can be well tolerated for many years; however, patients eventually develop symptoms and multi-organ dysfunction related to chronically elevated central venous pressure (Stout et al. 2019). Surgical repair for tricuspid valve dysfunction includes the placement of annular bands or rings (Aboulhosn et al. 2017) as well as more complex operations like the Cone repair to relocate or augment the tricuspid valve leaflets in patients with Ebstein's anomaly (Holst et al. 2018). Surgical valve replacement is typically performed with large diameter bioprostheses which are preferred over mechanical valve due to lower risk of thrombosis (Zhu et al. 2018; McElhinney et al. 2019; Garatti et al. 2012). Most bioprostheses require replacement within a decade due to progressive leaflet thickening and degeneration (Burri et al. 2016; Garatti et al. 2012). Valve replacement should be considered in those with dysfunctional valves who have signs or symptoms of elevated central venous pressure, low cardiac output, or atrial arrhythmias (Stout et al. 2019).

Transcatheter tricuspid valve replacement (TTVR) using balloon expandable platforms (Melody or Sapien) can be performed within dysfunctional bioprosthesis or surgically placed bands and rings (Ghobrial and Aboulhosn 2018; Aboulhosn et al. 2017; McElhinney et al. 2016b, 2019). The procedural success rate is high and short-term hemodynamic benefits are evident. A registry of 306 patients undergoing TTVR demonstrated a cumulative 3-year incidence of death of 17%, reintervention of 12%, and valve-related adverse outcomes (endocarditis, thrombosis, or dysfunction) of 8%. Eight of the patients (2.6%) developed valve thrombosis during the study follow-up (McElhinney et al. 2019). Perivalvular regurgitation is common when TTVR is performed in surgical bands and rings but can be managed using occlusion devices (Aboulhosn et al. 2017).

Mitral Valve

Congenital mitral valve disease results in stenotic, regurgitant, or mixed disease. Mitral ste-

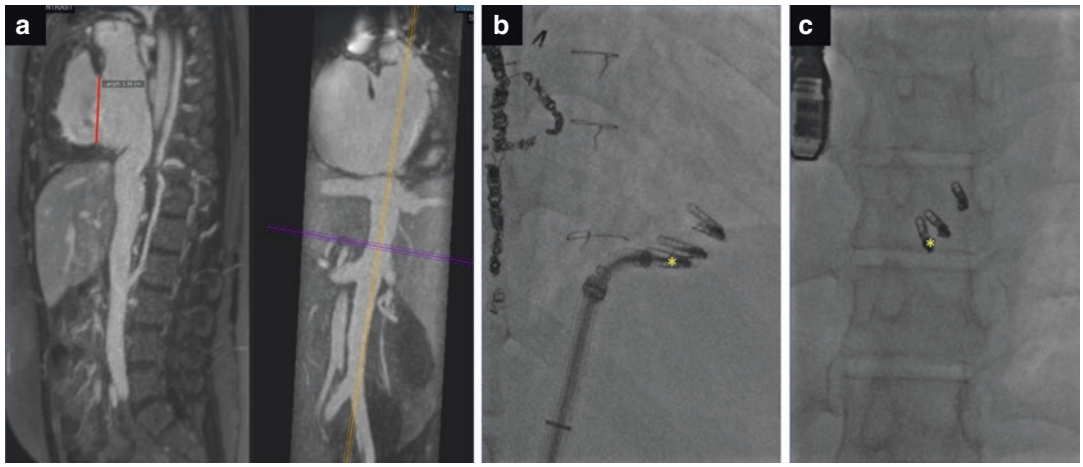

Fig. 12 Transcatheter Edge-to-Edge Repair using a Mitraclip in a Patient with Adult Congenital Heart Disease. (**a**) Sagittal and coronal magnetic resonance angiographic views of the inferior vena cava, common atrium, and common atrioventricular valve in a patient with a complete AV canal defect and single ventricle physiology. (**b**) Fluoroscopic image of the third Mitraclip (Abbott Laboratories, Chicago, IL) device being deployed to complete a transcatheter edge-to-edge repair of a common atrioventricular valve for severe atrioventricular valvular regurgitation. (**c**) Final fluoroscopic image of the three Mitraclips in stable position. * = Mitraclip

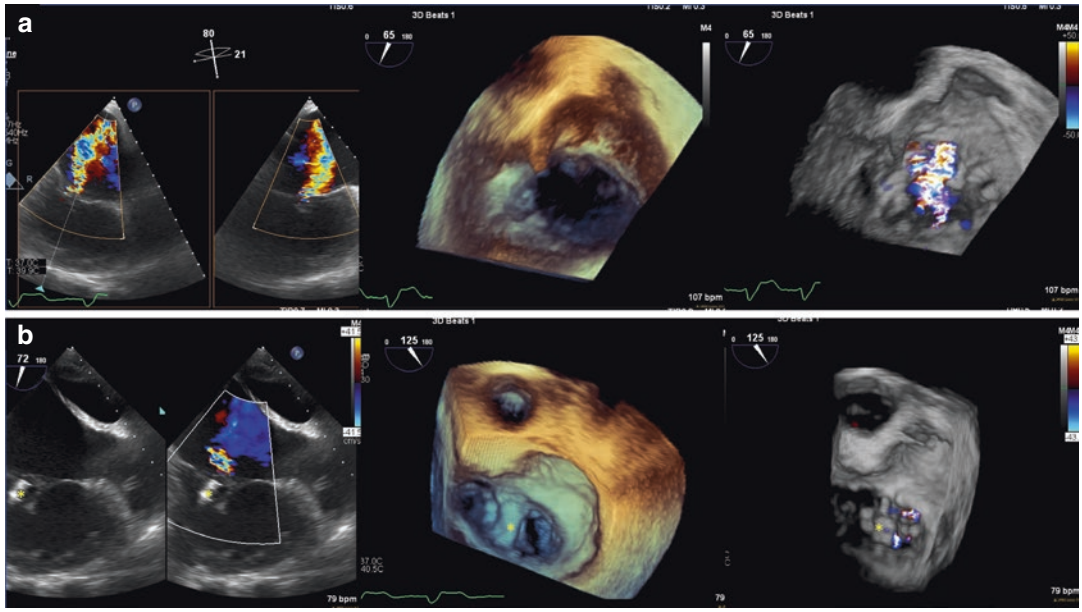

Fig. 13 Transcatheter Edge-to-Edge Repair using a Mitraclip in a Patient with Adult Congenital Heart Disease (Transesophageal Echocardiography Images). (**a**) Baseline transesophageal echocardiography (TEE) images of the Mitraclip procedure in a patient with severe common atrioventricular valvular regurgitation and single ventricle physiology. The left pane shows 2-dimensional X-plane color Doppler images of the valve with severe regurgitation. The middle pane is a 3-dimensional TEE image of the valve, and the right pane is a 3-dimensional color Doppler image of the valve demonstrating severe regurgitation. (**b**) TEE images after the Mitraclip procedure. The left pane is a 2-dimensional X-plane color Doppler image of the valve with only mild regurgitation. The middle pane is a 3-dimensional TEE image of the valve with a double-orifice after edge-to-edge repair. The right pane is a 3-dimensional color Doppler image of the valve with only mild residual regurgitation. * = Mitraclip

nosis may occur at the subvalvular, valvular, annular, or supra-annular levels (Ghobrial and Aboulhosn 2018). Mitral regurgitation may be primarily due to inherent anatomic abnormalities (e.g., clefts, myxomatous degeneration, chordal rupture) or secondarily due to progressive annular dilation related to left ventricular dysfunction. Indications for mitral valve surgery in ACHD patients are similar to those with non-congenital etiologies (Otto et al. 2020). Mitral valve repair is favored if feasible but mitral valve replacement is frequently required with either mechanical or bioprosthetic valves (Fiorilli et al. 2021; Choi et al. 2021). The durability of a bioprosthetic mitral valve is limited in the congenital population, evidenced by progressive dysfunction and freedom from valve replacement of only 44% at 10 years in one study (Choi et al. 2021).

Transcatheter mitral valve replacement (TMVR) is a rapidly advancing field with numerous devices being evaluated in clinical trials (Bapat et al. 2018; Del Val et al. 2019). Most procedures performed are in the valve-in-valve and valve-in-ring population (Paradis et al. 2015) and in those with calcified mitral annuli to allow for anchoring (Ghobrial and Aboulhosn 2018; Paradis et al. 2015). The approach to TMVR can be transvenous/transseptal or transapical; as with mitral repair techniques, transesophageal echocardiographic guidance is utilized (Fiorilli et al. 2021; Paradis et al. 2015) (See Fig. 14). Procedures are typically performed under general anesthesia (Paradis et al. 2015). In appropriately

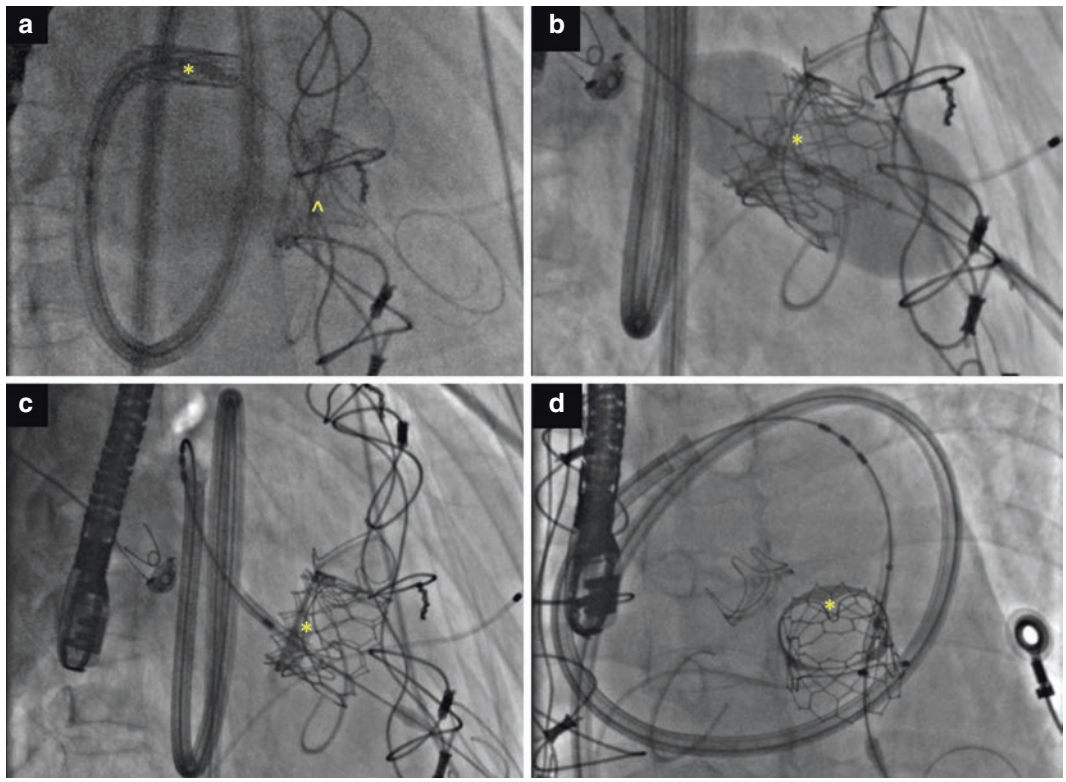

Fig. 14 Transcatheter Mitral Valve-in-Valve Replacement. (**a**) Transcatheter mitral valve-in-valve replacement using an Edwards Sapien 3 (Edwards Lifesciences, Irvine, CA) delivery system via transseptal access. The delivery system is seen looping around the large left atrium and tracking along a stiff wire that is across the prosthetic pulmonary valve and into the left ventricle. (**b**) Once the valve is seated across the prosthesis, the balloon is then inflated to deploy the fresh valve within the old mitral prosthesis. (**c**) The Edwards Sapien 3 valve is fully deployed within the old mitral prosthesis in stable position. (**d**) Final fluoroscopic image of the valve in a left anterior oblique projection

selected patients, the technical success rate is high but left ventricular outflow tract obstruction is a major concern, especially in those with native mitral valve tissue (Yoon et al. 2019). Trials for development of transcatheter valve delivery systems meant specifically for the mitral valve are currently ongoing for both transapical and transseptal approaches (Fiorilli et al. 2021; Del Val et al. 2019).

Aortic Valve Replacement

Aortic valve abnormalities are common in ACHD patients with resultant aortic stenosis (AS) and/or aortic regurgitation (AR), due to either primary valvular anatomic abnormalities or secondary to aortic dilation, sub-aortic stenosis, ventricular septal defects, or infection. The spectrum of clinical disease of AS varies from bicuspid aortic valve causing isolated disease to complex lesions that may involve multiple levels of hypoplasia or stenosis. The estimated prevalence of congenital aortic stenosis is between 1.1 to 4.9 per 10,000 live births (Marelli et al. 2014; Reller et al. 2008). Aortic valve surgery may include valve repair, valve replacement with a pulmonary autograft (Ross procedure), valve replacement with bioprosthesis or valve replacement with a mechanical prosthesis. Bioprosthetic valve degeneration is inevitable over time and occurs more quickly in younger patients (Fuller et al. 2021). Symptomatic patients or asymptomatic patients with evidence of ventricular dysfunction or severe enlargement should be considered for aortic valve intervention (Otto et al. 2020).

Transcatheter aortic valve replacement (TAVR) has become a widely used alternative to surgical aortic valve replacement predominantly in patients with calcific aortic valve stenosis, with overall good outcomes (Mack et al. 2019). Complications may occur and include paravalve leaks, conduction system damage requiring pacemaker placement, valve embolization, vascular complications, coronary ostial occlusion, aortic annular rupture, and stroke (Carroll et al. 2020). TAVR in patients with bicuspid aortic valve stenosis initially was associated with less optimal outcomes but results have improved dramatically over the past decade (Forrest et al. 2021) (Makkar et al. 2019; Yoon et al. 2020; Vincent et al. 2021). Patients with heavily calcified bicuspid valves have a higher incidence of complications (Yoon et al. 2020). For patients with predominantly regurgitant bicuspid valves, surgery is still recommended given the poor technical success rate of TAVR (Vincent et al. 2021). TAVR has been successfully performed in select cases of D-transposition of the great arteries status postarterial switch and valve sparing aortic root repair with recurrent AR (Ghobrial and Aboulhosn 2018), as well as those with existing bioprosthetic aortic valves (Paradis et al. 2015). Given the various anatomical variations and considerations, such as aortic root size, coronary artery anomalies, and aortic valve/annular calcification, a nuanced heart-team approach should be used for each congenital cardiac case with aortic stenosis/regurgitation to evaluate whether TAVR or SAVR would be the best option for that patient (Vincent et al. 2021).

Aortic Interventions

Balloon Angioplasty and Stenting of Coarctation of the Aorta

Coarctation of the aorta accounts for 2–5% of all congenital heart defects (Marelli et al. 2014; Reller et al. 2008) and is defined as narrowing of the distal aortic arch and/or proximal descending thoracic aorta, usually at the insertion point of the ductus arteriosus. Although the majority of cases are sporadic, there are certain genetic conditions such as Turner syndrome that are associated with this condition (Wong et al. 2014). Coarctation of the aorta usually occurs in conjunction with bicuspid aortic valves in ~50% of patients (Teo et al. 2011). Intracranial arterial aneurysms are present in ~10% of adults with coarctation (Curtis et al. 2012).

In patients with very severe coarctation or interruption of the aorta, clinical presentation with heart failure or cardiogenic shock is often at birth or shortly thereafter as ductus arteriosus starts to close. In less severe forms patients may

be asymptomatic and can present with difficult to control systemic hypertension. The natural history of coarctation of the aorta is concerning with greater than 50% mortality rate by the fourth decade of life (Jenkins and Ward 1999). The 2018 ACC/AHA Guidelines for Management of Patients with ACHD recommend surgical or transcatheter treatment in those with hypertension, the presence of anatomic aortic narrowing, and a significant gradient across the coarctation (upper/lower extremity resting cath peak-to-peak gradient >20 mmHg, mean echo Doppler gradient >20 mmHg, or upper/lower extremity resting peak-to-peak gradient >10 mmHg, mean Doppler gradient >10 mmHg in the presence of decreased LV function, aortic regurgitation, or collateral flow) (Stout et al. 2019). Effective relief of aortic obstruction is associated with significant improvement in long-term survival (Tennant et al. 2010).

Transcatheter intervention is more challenging in those with hypoplastic aortic arch, genetic conditions (e.g., Turner syndrome), or highly tortuous lesions. Transcatheter balloon angioplasty of aortic coarctation was initially performed in 1982 by Singer et al. (1982) and although immediate success rate is high, aortic wall complications can occur in 10% and re-obstruction develops in 32% of patients (Forbes et al. 2011). Given these concerns with angioplasty alone, stent implantation has supplanted angioplasty along since it was first reported by Suarez de Lezo et al. (1995). The procedure is typically performed under general anesthesia with the patient's arms positioned above the head to allow appropriate visualization of the aorta from a lateral view (See Fig. 15). The immediate results are excellent with a low risk of complications (<5%) and a low risk of aortic wall injury (3.1%), mild residual stenosis may occur (Forbes et al. 2011). Intermediate results from one study demonstrated that 4% of patients with stenting of the CoA had an unplanned reintervention due to recurrent coarctation or pseudoaneurysm formation, with an average time to reintervention of 2.84 years (Forbes et al. 2011). The availability of covered balloon and self-expanding stent platforms may further improve the safety profile (Taggart et al. 2016); however, an early comparison of uncovered vs. covered stents did not demonstrate significant differences in outcomes (Sohrabi et al. 2014).

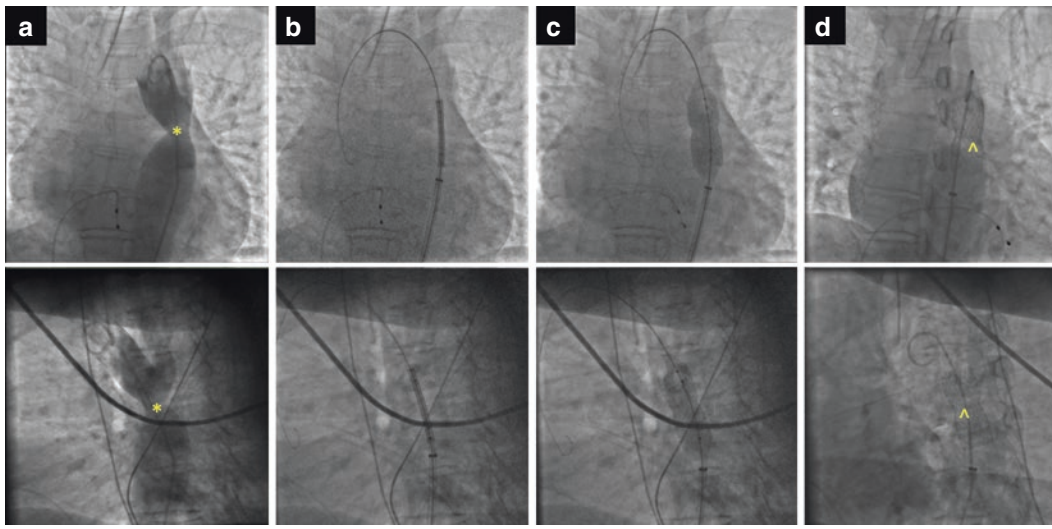

Fig. 15 Stenting of a Coarctation of the Aorta. Each panel is a biplane image with the top pane as the anterior-posterior projection and the bottom pane as the lateral projection. (**a**) Angiogram of the coarctation of the aorta. (**b**) Delivery of the stent over a stiff wire, which is across the coarctation and in the ascending aorta. (**c**) Balloon inflation of the stent across the coarctation. Note the waist at the coarctation site. (**d**) Final fluoroscopic image of the stent, demonstrating stable position of the stent and a mild residual waist at the coarctation. * = coarctation of the aorta, ^ = stented coarctation of the aorta

Pulmonary Artery Interventions

Balloon Angioplasty and Stenting of Pulmonary Artery Stenosis

Stenosis of the proximal or branch pulmonary arteries very rarely occurs in isolation but is typically associated with other lesions as in tetralogy of Fallot, Alagille Syndrome, Williams syndrome, Noonan syndrome, or congenital rubella syndrome (Ngo et al. 2014; Tonelli et al. 2015). Stenosis may also be associated with surgical shunt placement.

Treatment of pulmonary artery stenosis is indicated if there are symptoms associated with evidence of right ventricular pressure elevation or reduced lung perfusion (Zablah and Morgan 2019). Surgical treatment of proximal lesions is associated with excellent outcomes, but peripheral stenoses are less amenable to surgical intervention. Lock et al. first described a percutaneous static balloon angioplasty technique for the treatment of peripheral pulmonary artery stenosis in 1983 (Lock et al. 1983). An adequate result depends on the use of sufficiently large high-pressure balloons that tear the vascular intima and part of the media, leaving a slim safety margin for this procedure (Nakanishi et al. 1999). As with balloon angioplasty alone of other arterial stenoses, restenosis rates are high prompting the employment of stent platforms to maintain patency (Zablah and Morgan 2019; Nakanishi 2001). The first and second arcade branches of the pulmonary arteries can be effectively treated with stents; more distal stenoses may not be amenable to stenting and thus balloon angioplasty alone is performed. Patients with multiple distal stenoses often require multiple balloon dilations (Zablah and Morgan 2019). Proximal or ostial branch pulmonary artery stenoses may require simultaneous bifurcation stent implantation (Zablah and Morgan 2019). Major complications occurred in 9% of all pulmonary artery stenting procedures in the IMPACT registry. Patients weighing less than 4 kg, emergency procedures, and single ventricle status were significantly associated with the risk of any adverse event, which included vessel rupture, stent embolization, and death (Zablah and Morgan 2019). Another study reported a complication rate of 3% with no deaths in their cohort of 183 patients (Nakanishi 2001).

Closure of Paravalvular Leaks

The growing number of surgically or transcatheter placed valves in ACHD patients inevitably results in an increasing number of patients with paravalvular regurgitation (PVL) which affects 5–17% of surgically placed valves (Ruiz et al. 2017; Goel and Eleid 2018). PVL may occur in TAVR patients, but the incidence has reduced to between 2 and 5% for the newer generation of transcatheter aortic valve implants (Goel and Eleid 2018). Patients with mild paravalvular regurgitation can be managed conservatively, but those with heart failure, hemolytic anemia, or signs of ventricular dilation from volume overload have an indication for closure of the paravalvular leak (Ruiz et al. 2017; Goel and Eleid 2018; Giblett et al. 2019). Since mortality for surgical closure of PVL may approach 7–11%, the preference for most patients should be to attempt a percutaneous approach first (Ruiz et al. 2017).

Transesophageal echocardiography (TEE), as well as ECG-gated computed tomography angiography, is used to fully characterize the anatomy of the leak. PVL can occur in any valve position (Aboulhosn et al. 2017; Ruiz et al. 2017; Seery and Slack 2014) and the imaging modality used for each procedure can vary from intracardiac echo (ICE) in those with right-sided PVL to TEE in left-sided PVL (Tan and Aboulhosn 2019). That being said, most procedures are performed under TEE guidance and general anesthesia for patient comfort (Goel and Eleid 2018; Giblett et al. 2019). The procedure generally consists of crossing the area of the paravalvular leak with a wire and catheter, and then exchanging the catheter for a delivery sheath that can deploy various plugs to occlude the leak (Goel and Eleid 2018; Giblett et al. 2019). Depending on the location of the leak

and the valve involved, the procedure may also require transseptal puncture, transapical puncture, or creation of an arteriovenous loop (Goel and Eleid 2018; Giblett et al. 2019). A wide variety of occlusion devices have been used to treat PVL, including the Amplatzer Vascular Plug 2 (AVP2, Abbott Laboratories, Chicago, IL), the Amplatzer Vascular Plug 4 (AVP4, Abbott Laboratories, Chicago, IL), the muscular VSD occluder (Abbott Laboratories, Chicago, IL), or the Amplatzer Ductal Occluder (Abbott, Laboratories, Chicago, IL), among others (Goel and Eleid 2018; Giblett et al. 2019; Seery and Slack 2014) (Figs. 16 and 17).

Procedural success is generally high, with some studies citing >90% successful device implantation, with reduction in the leak to mild or none in >75% of patients (Sorajja et al. 2011). Closure of PVL that results in a meaningful reduction in the severity of the leak leads to improved outcomes, specifically with improvements in mortality and functional class (Goel and Eleid 2018; Millán et al. 2015). Complications from PVL closure, however, can occur, and include prosthetic leaflet impingement, especially in mechanical valves, device embolization, bleeding, need for emergent surgery, cardiac tamponade, hemolytic anemia, stroke, acute kidney injury, device thrombosis, and infectious endocarditis (Ruiz et al. 2017; Goel and Eleid 2018; Sorajja et al. 2011). Patients with more severe residual paravalvular leak after a PVL occlusion procedure had higher rates of complications, including mortality and hemolytic anemia, suggesting that the procedure must significantly occlude the leak before any improvement in outcomes can be observed (Sorajja et al. 2011).

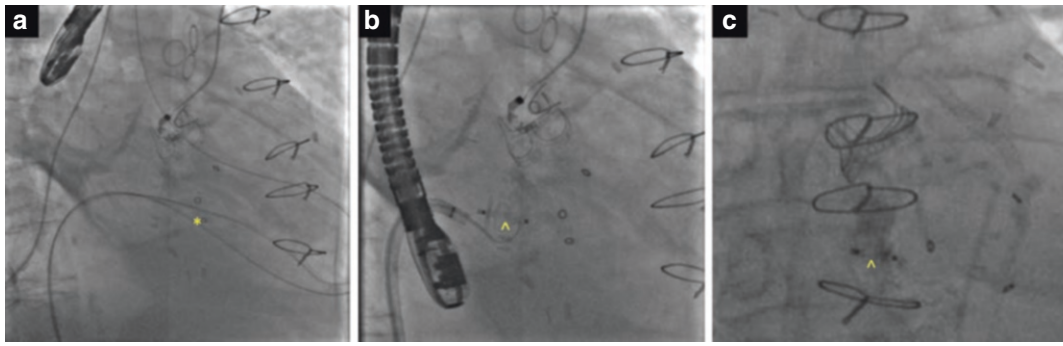

Fig. 16 Transcatheter occlusion of a paravalvular leak (Fluoroscopic images). (**a**) Fluoroscopic image of a paravalvular leak of a mitral prosthesis. There are two wires across the leak and one wire is exiting the left ventricle through the prosthetic aortic valve. (**b**) An AVP-II device is deployed across the site of paravalvular leak. A wire is across the residual leak, but no equipment was able to be delivered across the leak since the defect was very small. (**c**) The decision was made to just deploy one device, and there was only a trace paravalvular leak on transesophageal imaging. * = location of the paravalvular leak, ^ = AVP-II device

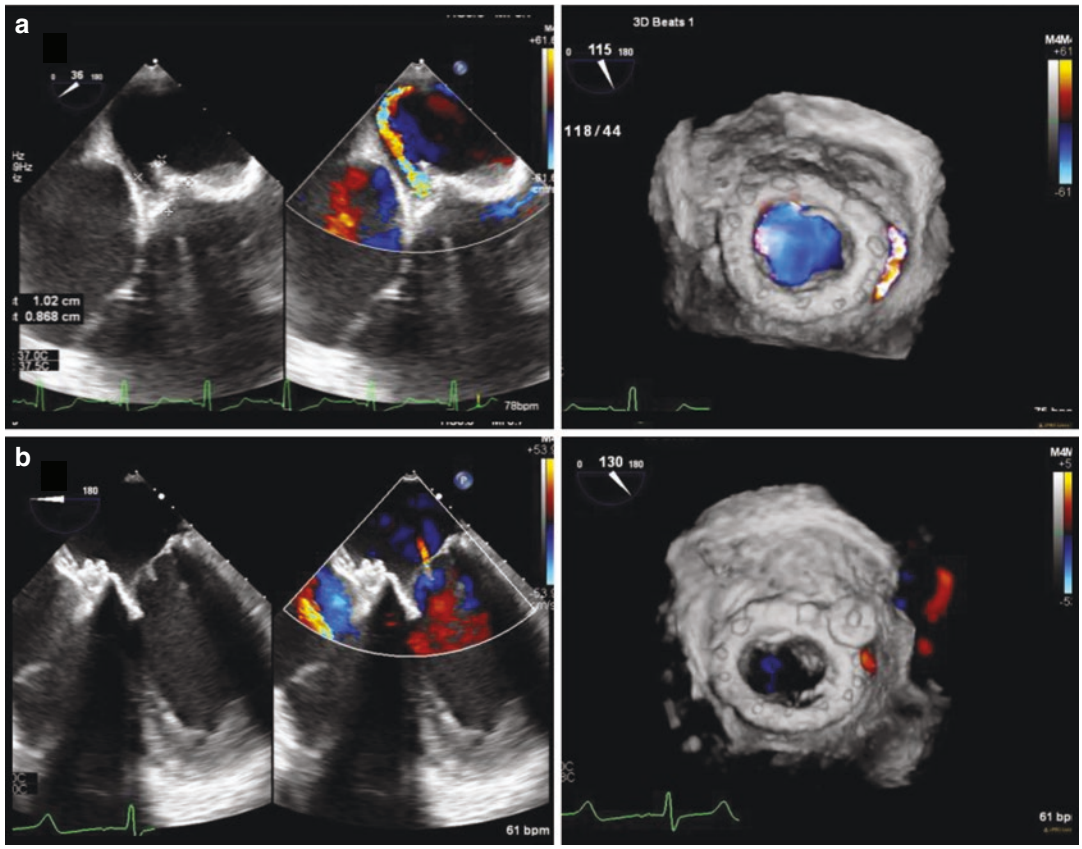

Fig. 17 Transcatheter occlusion of a paravalvular leak (Transesophageal echocardiography images). (**a**) Transesophageal echocardiography (TEE) images of the paravalvular leak at baseline. The left pane is a 2-dimensional and color Doppler image of the leak. The right pane is a 3-dimensional color Doppler image demonstrating the leak along the medial aspect of the mitral prosthesis. (**b**) TEE images of the paravalvular leak after device occlusion. The left pane is a 2-dimensional and color Doppler image of the device seated across the site of the leak with no appreciable flow across the device. The right pane is a 3-dimensional color Doppler image demonstrating stable positioning of the device and only trace flow through a residual defect just inferior to the device. * = site of paravalvular leak, ^ = AVP-II device

Special Populations

Single Ventricle Patients (Fontan Procedure)

Single ventricle physiology is present in 1–1.5 per 10,000 live births in some studies (Marelli et al. 2014; Reller et al. 2008). Refinement of the Fontan operation and medical advancements has led to improved short- and medium-term survival for patients with single ventricle physiology (Kotani et al. 2018). Nevertheless, freedom from late complications of the Fontan procedure is low, and one study observed that 50% of patients with a Fontan circulation suffered a complication related to the Fontan circuit over a period of 20 years (Kotani et al. 2018). Fontan patients may present with various multi-system complications that require hospitalization, including arrhythmias, heart failure, thromboembolism, protein-losing enteropathy (PLE), plastic bronchitis, cyanosis due to venous collaterals, liver dysfunction, and renal failure, among others (Kotani et al. 2018). In order to improve survival and quality of life, the majority of adult Fontan patients undergo diagnostic and interventional

catheterization. It is essential for the function of the Fontan circuit that there are no vascular anatomic obstructions within the Fontan pathway or the pulmonary arterial tree. Therefore, transcatheter stenting may be necessary to ensure unobstructed Fontan pathway. All pulmonary blood flows rely on a high systemic venous pressure driving flow through a low resistance circuit and any obstruction in this circuit, even if it is only a 1 mmHg gradient, may be hemodynamically significant.

Many Fontan patients will eventually develop heart failure and are referred for heart transplantation or even combined heart-liver transplantation. These patients will need a pre-operative catheterization in order to perform a liver biopsy for risk stratification, as well as pre-operative coil embolization/occlusion of significant aortopulmonary or venovenous collaterals that may lead to life-threatening perioperative bleeding during the transplant operation. Treatment of venovenous collaterals will improve cyanosis (Lluri et al. 2015) and prevent perioperative bleeding at the time of transplant, but at the expense of increased systemic venous pressure and reduction in systemic ventricular preload. Some studies show an increase in long-term mortality after these procedures (Poterucha et al. 2015); so coiling of venovenous collaterals need to be timed well with the transplant listing. Aortopulmonary collaterals increase pulmonary blood flow, but will chronically volume load the single ventricle, which may trigger ventricular remodeling and increased end-diastolic pressure. This eventually leads to ventricular dysfunction and failure. While practice variation varies across institutions (Banka et al. 2011), coiling of aortopulmonary collaterals is a very common procedure to relieve overcirculation, treat hemoptysis, and to prepare patients for transplant by reducing their perioperative bleeding risk (Reardon et al. 2021).

Some Fontan patients have Fontan failure related to abnormal lymphatic drainage, such as protein losing enteropathy and plastic bronchitis (Dori et al. 2016). Percutaneous lymphatic embolization is a novel and specialized technique to identify pathways of lymphatic decompression and occlude these abnormal channels to treat PLE and plastic bronchitis. Only a few centers are capable of specializing in these interventions, as it requires magnetic resonance lymphangiograms (Biko et al. 2019), but these procedures can be very effective.

Pregnant Patients

Patients with ACHD have more maternal and fetal morbidity and mortality compared to women without congenital heart disease (Ramage et al. 2019). Pregnancy is a stressful time for a woman's heart, as it leads to increased circulating blood volume and cardiac output that can lead to heart failure, arrhythmias, and other cardiac issues (Canobbio et al. 2017). It is rare for a congenital patient to need a transcatheter intervention while pregnant, but there have been reports of patients needing coarctation stenting (Ciresi et al. 2020) and atrial septal defect closure (Bredy et al. 2018). Should there be a need for an transcatheter intervention during pregnancy, great care should be taken to minimize radiation exposure during the case (Canobbio et al. 2017). Use of imaging techniques like ICE and TEE may be helpful in reducing the amount of fluoroscopy needed for such interventions.

Hybrid Procedures

There are many ACHD patients that pose an increased surgical risk for cardiopulmonary bypass, especially those with severe ventricular dysfunction, multi-organ dysfunction, and pulmonary hypertension. Others may have increased risk of sternotomy such as those with multiple prior sternotomies and direct apposition of the aorta or cardiac chambers to the sternum. In such patients, hybrid approaches that either avoid cardiopulmonary bypass or provide surgical access via non-sternotomy approaches may be beneficial. Occasionally, due to limited vascular access or severely tortuous and challenging vascular anatomy, a hybrid surgical approach is preferred to provide direct access for transcatheter intervention. Hybrid approaches have long been a staple of

congenital interventions in the pediatric world, mainly due to the small size of the vascular structures in children that limits the use of vascular access to deliver interventional equipment (Holoshitz et al. 2014). Hybrid approaches like stenting of the ductus arteriosus and concomitant banding of the pulmonary arteries, closure of a ventricular septal defect via a right ventricular puncture, or transcatheter valve replacement via ventricular access have all been described (Holoshitz et al. 2014). In adults with congenital heart disease, hybrid approaches have been used to perform transcatheter valve replacement of the pulmonary valve in patients with large right ventricular outflow tracts (Sosnowski et al. 2016; Porras et al. 2015), transcatheter mitral valve replacements in those with difficult anatomy for a transseptal approach (Harloff et al. 2020), or even for paravalvular leak occlusion of the mitral valve via transapical access (Lang et al. 2010; Nijenhuis et al. 2014). While these procedures sometimes require a sternotomy or a smaller chest incision, the use of cardiopulmonary bypass is minimized with hybrid procedures, which leads to reduced blood transfusion requirements compared to surgery (Sosnowski et al. 2016). Nevertheless, hybrid procedures can lead to increased bleeding compared to just transcatheter procedures, and one series had a bleeding complication rate of 19% at 30 days (Nijenhuis et al. 2014). Hybrid procedures, however, can be a feasible option for certain high-risk ACHD patients who need interventions, especially at centers with a strong working relationship between the interventional cardiologist and cardiothoracic surgeon (Holmes et al. 2013).

Conclusion

In summary, the field of transcatheter interventions for ACHD patients has evolved rapidly over the past 60 years. Patients can now receive therapies for vascular obstruction, valve dysfunction, intracardiac shunts, and lymphatic problems via nonsurgical and transcatheter techniques. As these patients grow older and develop more sequelae from their residual defects, more patients will need transcatheter interventions. Understanding the rationale, steps, and potential risks/complications of these interventions will prepare the anesthesiologist for safer perioperative management of these patients.

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Postoperative Cardiovascular and Hemodynamic Management in Congenital Cardiac Surgery

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Abstract

In congenital heart surgery, postoperative cardiovascular and hemodynamic management is one of the cornerstones of care, while taking an inappropriate approach to this task could significantly impair the whole outcome.

This chapter deals with a general overview of the main aspects of postoperative cardiovascular and hemodynamic management, mainly including:

- Transferring patient from operating room
- Monitoring techniques
- Hemodynamic complications
- Postoperative bleeding and cardiac tamponade
- Pulmonary hypertension

Nowadays, several novel monitoring devices have been introduced to clinical practice in an attempt to improve the final outcome, with some being more efficacious than others; however, the principles of care remain constant, and clinical assessment and robust decision making still remain the cornerstone of postoperative cardiovascular and hemodynamic management.

Keywords

Postoperative care · Cardiovascular Monitoring · Hemodynamic · Congenital Heart · Anesthesia · Surgery · Intensive care

Introduction

Care of postoperative cardiac patients needs consideration of the patient as a whole. Management of the cardiovascular system is the main duty of intensive care specialists.

Meticulous postoperative care requires comprehensive information on the preoperative diagnosis and condition as well as the details of surgical repair. In this regard, intensivists should have close communication and collaboration with the operating room team.

In this chapter, we first review the important hemodynamic parameters measured by monitoring techniques and then describe some important postoperative complications related to the cardiovascular system.

Transferring Patient from Operating Room

Postoperative care starts from the point when the operating room team decides to transfer the patient to the pediatric intensive care unit (ICU). This is a very critical phase because various prob-

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lems such as inadvertent alteration in the rate of drug infusion, displacement of the endotracheal tube, or hypothermia may result in deterioration of the patient's condition. This process needs a "Multidisciplinary Human-Centered Design Approach" to improve the quality of care and the clinical outcome (Segall et al. 2016).

The ICU team should be aware in advance of the hemodynamic state of the patient, medications, and the type and setting of the ventilator support (Mistry et al. 2008; Schlachta-Fairchild et al. 2008; Collins et al. 2011; Agha 2012).

The handover of the surgical patient from the operating room staff to the ICU staff should be conducted by a standardized process. The handover is given usually by the anesthesiologist who discusses every related issue like airway and invasive lines, information about the cardiopulmonary bypass, performed procedure, intraoperative echocardiographic findings, inotropes, etc. All staff should be present during the handoff process (Joy et al. 2011; Saarijärvi et al. 2019; Hart et al. 2020).

Monitoring Techniques

To manage the hemodynamic state, intensivist uses different monitoring techniques. The level of monitoring depends on the preoperative diagnosis and the type of surgical repair or palliation. Some monitoring methods are performed for all patients. These include continuous ECG, systemic arterial pressure, peripheral pulse oximetry, respiratory rate, and end-tidal CO_2.

Arterial oxygen saturation can be evaluated by pulse oximetry. Although pulse oximetry is an easy and noninvasive technique, it has important limitations. It works well only when there is good peripheral perfusion and in the case of severe hypoxemia, it would not be accurate (Carter et al. 1998). In these conditions, PaO_2 and SpO_2 measured from an arterial blood gas sample are more reliable. The audience is suggested to refer to chapters "Perioperative Respiratory Monitoring in Congenital Heart Disease Patients" and "Postoperative Respiratory Management in Pediatric Cardiac Surgical Patients" of this book for more detailed discussions about respiratory monitoring and management.

Near-infrared spectroscopy (NIRS), a marker of tissue oxygenation is based on arterial and predominantly venous oxygen saturation. NIRS is correlated with cardiac output and oxygen consumption (Hirsch et al. 2009). Today, this monitoring method is routinely used in most cardiac surgery centers worldwide. More detailed discussions could be found in chapter "Central Nervous System Monitoring in Pediatric Cardiac Surgery" and "Postoperative Central Nervous System Management in Congenital Cardiac Surgical Patients" of this book regarding neurologic monitoring and management.

Based on the underlying disease and the performed procedure, some invasive monitoring techniques are utilized. All of the parameters are achieved through the intracardiac lines.

A central venous catheter is routinely inserted for all cardiac surgeries, except for some simple palliative procedures. Central venous pressure (CVP), which is equal to the mean right atrial pressure (RAP), indicates the preload status. Bleeding, hypovolemia, or peripheral vasodilation would decrease CVP, and conversely, cardiac tamponade or right ventricular dysfunction would increase CVP. Oxygen saturation of blood samples drawn through a central venous catheter could be very helpful for hemodynamic management. For example, any residual left-to-right shunt at the atrial level or anomalous pulmonary venous connection can abnormally rise right atrial oxygen saturation. Increased oxygen consumption due to low cardiac output or severe anemia causes reduced right atrial oxygen saturation.

Today, a pulmonary artery (PA) catheter is inserted less frequently, but it remains useful in the management of patients with pulmonary arterial or venous hypertension (Del Cerro et al. 2016). The mean PA pressure is elevated initially after weaning from cardiopulmonary bypass, but it should be less than 25 mmHg. In patients with pulmonary hypertension before surgery, mean PA pressure is usually more than 25 mmHg. The relationship of the PA pressure to the systemic pressure may be more helpful than the absolute

values. If this ratio is greater than 50%, a complete evaluation of various parameters such as ventricular function, cardiac output, systemic vascular resistance, and pulmonary vascular resistance should be performed. Finally, the same conditions that alter the oxygen saturation of the right atrium can influence the oxygen saturation of the pulmonary artery in the same manner.

The left atrial (LA) catheter is simple and very useful in the management of mitral valve or left ventricular dysfunction. LA pressure is normally about 2 mmHg greater than CVP and demonstrates the preload status of the left ventricle (Kouchoukos et al. 1971; Arnaz and Altun 2018). There are different causes of abnormally elevated LA pressure after cardiac surgery. Left ventricular dysfunction or hypertrophy, myocardial ischemia, mitral valve disease, large left-to-right shunt, and cardiac tamponade are among them (Wernovsky et al. 1995; Krishnamoorthy et al. 2021). It should be mentioned that alteration of LA oxygen saturation could indicate a serious problem. Reduced LA oxygen saturation can be the result of an atrial level right-to-left shunt or severe parenchymal lung disease with pulmonary venous desaturation (Eleid et al. 2018). The interested reader could find detailed discussions regarding hemodynamic monitoring in chapter "Pediatric Cardiovascular Monitoring" of this book.

Hemodynamic Complications

Low Cardiac Output

A significant percentage of patients experience low cardiac output (LCO) postoperatively, the number of which relates to the type of procedure and patient's condition. LCO usually occurs within 6–12 h after surgery (Wernovsky et al. 1995; Chandler and Kirsch 2016; Du et al. 2020).

There are clinical signs or paraclinical parameters that help us to assess the cardiac output. These include the skin color and temperature, capillary refill, urine output, systemic arterial pressure, right and left atrial filling pressures, acid–base status, and peripheral O2 saturation measured by pulse oximetry (Kirklin et al. 1981).

In the early stages of decreased cardiac output, the changes are subtle. The skin temperature and capillary refill decrease, especially in the extremities. The urine output that should be at least 1 mL/kg/h diminishes to an oliguric level. Metabolic acidosis with the elevation of lactate level occurs. The pulse oximetry shows a decreasing trend in O_2 saturation level. The filling pressures of the right and left atrium may be decreased (excessive bleeding) or increased (myocardial dysfunction or tamponade). At last, the syndrome of LCO completes with the fall in systemic arterial pressure.

LCO may be caused by one or a combination of the following factors (Du et al. 2020):

1. Residual intracardiac lesion
2. Factors related to the surgical procedure
3. Insufficient preload due to loss of intravascular volume
4. Excessive afterload due to vasoconstriction
5. Contractility dysfunction
6. Heart rate or rhythm changes
7. Myocardial preservation method

Residual Defects

Any important residual defect can influence the postoperative course by its hemodynamic derangement. Residual lesions could be found by auscultation, intracardiac pressure, or arterial pressure monitoring and oxygen saturation data. For example, wide pulse pressure and the diastolic murmur may be due to significant aortic regurgitation following aortic valve repair. Further evaluation with echocardiography and/or cardiac catheterization should be performed in the case of compromising ventricular function.

Surgical-Related Factors

These factors are classified into two general groups. The first group consists of factors related to the surgical technique itself. For example, ventriculotomy could result in ventricular dysfunction postoperatively. Injury to the conduction system (sinoatrial or atrioventricular node) dur-

ing surgery for VSD closure or repair of a sinus venosus ASD definitively influences the postoperative course. Ongoing bleeding after cardiac surgery may expose the patient not only to the risk of cardiac tamponade but also to the inflammatory response due to transfusion of blood products (Chandler and Kirsch 2016; Du et al. 2020; Song et al. 2021).

The second group of factors is related to CPB and myocardial ischemia during cardiac surgery. The CPB with its unique exposure of blood components to the extracorporeal circuit may induce an immense systemic inflammatory response. This response, which is magnified in children due to the large bypass circuit, includes humoral and cellular reactions that finally result in the release of vasoactive substances and inflammatory mediators (Burrows et al. 1988).

Increased interstitial fluid and multiorgan failure (including heart and lung) are the results of this systemic inflammatory response (Du et al. 2020; Song et al. 2021).

Myocardial injury may occur because of problems with cardioplegic protection, inadequate hypothermia, intracoronary air embolism, or insufficient coronary perfusion. Myocardial ischemia may present with a sudden onset of fatal dysrhythmia or complete heart block rather than ECG changes in the ST segment.

Preload

The usual monitoring method to evaluate preload is the central venous pressure (CVP) or mean atrial pressure. Initially, after surgery and CPB, the filling pressures are normal or slightly elevated. As the patient continues to rewarm and vasodilate, these pressures and consequently systemic blood pressure tend to be decreased. In this stage, intravascular volume infusion is necessary to maintain systemic pressure in the normal range (Friedman and George 1985).

Preload should be maintained higher in patients with noncompliant or hypertrophic ventricles and also in patients who are dependent on complete mixing at the atrial level.

Afterload

Elevated afterload is frequently seen after cardiac surgery with CPB. It may occur in both systemic and pulmonary circulation. Increased afterload is caused by elevated systemic vascular resistance. This phenomenon results in decreased peripheral perfusion, which is manifested clinically by cool extremities and low urine output (Lehot et al. 1992).

High afterload is tolerated less well in neonates than in older infants and children, so they benefit from afterload reduction therapy. The clinician should recognize and improve conditions like pain and hypothermia, which exacerbate vasoconstriction as well as utilizing a vasodilating agent. Phosphodiesterase inhibitors (e.g., milrinone) and nitric compounds are used in combination with inotropic agents to reduce afterload and augment cardiac output (Stocker et al. 2007; Burkhardt et al. 2015).

Contractility Dysfunction

Cardiac contractility is the ability of the myocardium to generate a force, which is a load-independent property. Contractility dysfunction may be originated from preoperative, intraoperative, or postoperative factors. Pressure or volume overload, myocardial ischemia, anesthesia, hypoxia, acidosis, and various pharmacologic agents can depress cardiac contractility.

If low cardiac output persists after heart rate, preload and afterload are optimized, cardiac contractility should be reinforced by inotropic drugs. It seems that stating inotropic support in the operating room is better than waiting for the signs of low cardiac output to appear.

There are several inotropic agents, and each has its characteristic effects. The commonly used drugs in practice are dopamine, dobutamine, epinephrine, milrinone, isoproterenol, and norepinephrine.

Dopamine has effects on both α and β adrenergic receptors. The dose range of 2–5 μg/kg/min can increase renal blood flow by dilation of splanchnic vessels. Doses in the range of 5–10 μg/

kg/min tend to enhance cardiac contractility by stimulation of myocardial β adrenergic receptors. Dopamine in the range of 10–20 μg/kg/min stimulates α receptors and causes peripheral and pulmonary vasoconstriction. It appears that the neonatal myocardium is less sensitive to the dopamine effect than that of older children (Driscoll et al. 1979).

Dobutamine is almost specific for cardiac β receptors. It can increase cardiac contractility without increasing systemic or pulmonary vascular resistance (Loeb et al. 1977). Its usual dose range is 2–10 μg/kg/min. Some patients respond to dobutamine with extreme tachycardia. Dobutamine is contraindicated when there is systemic hypotension.

Isoproterenol is a strong inotropic and chronotropic agent. It acts as a selective β agonist. Isoproterenol causes peripheral and pulmonary vasodilation. Its usage is limited by tachycardia and oxygen consumption.

Epinephrine is usually utilized for patients with severe myocardial dysfunction. The dose range is 0.05–0.5 μg/kg/min. Epinephrine in lower doses causes increasing contractility and decreasing afterload by vasodilation (β agonist), while in higher doses causes severe peripheral vasoconstriction (α agonist). Epinephrine is not frequently used with doses higher than 0.2 μg/kg/min because of its adverse effect on renal perfusion. Norepinephrine is a potent α agonist so it has systemic vasoconstriction and moderate inotropic effects.

Milrinone is a phosphodiesterase inhibitor that acts mainly by afterload reduction. It has also a positive inotropic effect. Milrinone is an ideal choice for patients with pulmonary hypertension because of its pulmonary vasodilatory effect; milrinone is contraindicated when there is systemic hypotension (Stocker et al. 2007; Burkhardt et al. 2015).

A combination of inotropic drugs should be considered in the management of patients with severe myocardial dysfunction or when side effects like systemic hypotension preclude the continuation of medication.

Dysrhythmia

ECG is an essential tool to identify whether the patient is in sinus rhythm postoperatively. Sinus rhythm by providing the atrioventricular synchrony as well as the contribution of atrial contraction is very important for maintaining cardiac output in the normal range, especially in the early postoperative period.

Sinus tachycardia must be differentiated from supraventricular, ventricular, or junctional tachycardia. Sinus tachycardia, which is a normal hemodynamic response, is usually related to an underlying condition like pain, anxiety, fever, or anemia. Some inotropic drugs like dopamine may induce severe tachycardia. Obviously, by relief of aggravating factors, heart rate would decrease.

Any tachyarrhythmia could influence negatively cardiac output (Hoffman et al. 2002b). They compromise the diastolic filling of ventricles or diminish their systolic function. The treatment plan consists of lowering the inotrope dosage, if possible, and antiarrhythmic drugs. Sometimes inducing mild hypothermia and atrioventricular sequential pacing may be beneficial (Hoffman et al. 2002a).

Postoperative Bleeding and Cardiac Tamponade

Excessive postoperative bleeding occurs in a very small percentage of patients. It is more frequent in deeply cyanotic patients, patients with preoperative severe ventricular dysfunction, and reoperations (Gomes and McGoon 1970).

Cardiopulmonary bypass results in several alterations in the coagulation system. Thrombocytopenia and platelet dysfunction, dilution of coagulation factors, and fibrinolysis are among the factors that prevent normal hemostatic function. Both inadequate heparin neutralization and protamine overdose can cause coagulation disorder. Sometimes multiple factors lead to the syndrome of disseminated intravascular coagulation (DIC), which is very difficult to control (Guay and Rivard 1996).

Treatment of bleeding starts from the point that the surgeon incises the skin. Gentle handling of tissue, use of proper sutures and prosthetic materials, secure tensionless suture lines, and meticulous hemostasis are the basic surgical principles to prevent postoperative bleeding. In the ICU, management of bleeding consists of correction of underlying coagulation disorder by replacement of deficient factors. Platelet should be transfused if there is thrombocytopenia (<50,000 platelet/mm^2). The use of fresh whole blood is very effective to reduce bleeding, especially in the neonatal population (Manno et al. 1991). If it is not available, the combination of fresh frozen plasma, platelet concentrate, and cryoprecipitate will be useful.

Surgical re-exploration is indicated whenever the amount of chest tube drainage passes a critical level or the signs of tamponade occurs. In the absence of coagulopathy, hourly drainage of more than 3 mL/kg for three consecutive hours or sudden drainage of more than 5 mL/kg in an hour are indications for re-exploration. Some surgeons consider re-exploration if the blood loss exceeds 10% of blood volume in 1 h or 20% in 4 h.

Continuous postoperative bleeding not effectively drained by the chest tubes results in cardiac tamponade. This complication should be suspected when chest tube drainage stops in a patient with previous significant bleeding. Cardiac tamponade due to cardiac chambers compression by blood clots is manifested by elevated venous pressure, paradoxical pulse and then narrow pulse pressure, reduction of urine output, and systemic hypotension. Arterial pressure decreases with minimal or no response to volume loading or increased dosage of inotropes. If not properly managed, tamponade quickly culminates in cardiac arrest.

Any patient suspected of having cardiac tamponade should be returned to the operating room. A rapidly deteriorating hemodynamic condition forces sternal opening to be done in the ICU. After the removal of clots, all surgical sites should be meticulously examined for the source of bleeding. The decision about closing the sternum or leaving it open depends on the hemodynamic state, cardiac dilatation, and myocardial swelling.

It is necessary to discuss two other forms of cardiac tamponade. The first, which is called dry tamponade, is seen in surgical patients with right ventricular dysfunction, frequently associated with pulmonary hypertension. The sudden increase in pulmonary arterial pressure leads to right ventricular dilatation, which is already dysfunctional and compressed by the closed space of the mediastinum. The signs of cardiac tamponade ensue and, if not relieved by sternal opening, can terminate in cardiac arrest. The second form is the delayed cardiac tamponade. It is a manifestation of the post-pericardiotomy syndrome and occurs from several days to a few weeks after cardiac surgery. When the pericardial effusion is sizable, with no response to anti-inflammatory drugs or corticosteroids, pericardial drainage by percutaneous or open methods is indicated (Horneffer et al. 1990).

The interested reader is addressed to chapter "Postoperative Bleeding and Coagulation Management in Congenital Cardiac Surgical Patients".

Pulmonary Hypertension

Pulmonary hypertension (PH) after cardiac surgery is one of the challenging problems encountered in the postoperative period. Patients who have left-to-right shunt or pulmonary venous obstruction preoperatively are prone to develop postoperative pulmonary hypertension (Hoffman et al. 1981).

PH is defined as the "progressive disease of the pulmonary vascular system, with a mean pulmonary artery pressure (mPAP) >20 mmHg at rest measured by right heart catheterization." Concurrent pulmonary arterial wedge pressure (PAWP) of ≤15 mmHg and pulmonary vascular resistance (PVR) of ≤3 Wood units/m^2 are the main indicators of precapillary pulmonary hypertension; this is the new definition from the Sixth World Symposium on Pulmonary Hypertension (WSPH) held in 2018. The previous definition of the WSPH, that is, mean pulmonary artery pressure (mPAP) of ≥25 mmHg at rest in the right heart catheterization as the threshold for PH is no

longer valid (Nemoto et al. 2019; Simonneau et al. 2019; Thomas et al. 2020).

Elevated pulmonary arterial pressure can produce significant morbidity. Increased afterload of the right ventricle leads to ventricular dysfunction and ultimately low cardiac output. Sometimes a sudden increase in pulmonary vascular resistance results in acute hemodynamic deterioration. This condition, which is termed pulmonary hypertensive crisis, could be a life-threatening problem and is manifested by the signs of low cardiac output, arterial desaturation, bradycardia, and cardiac arrest (Wheller et al. 1979). In patients with communication between systemic and pulmonary circulation, increased pulmonary vascular resistance results in right-to-left shunt and hypoxemia. It should be mentioned that various factors such as acidosis, rise in PaCO2, respiratory infection, and endotracheal suctioning can precipitate pulmonary hypertensive crisis.

Treatment of postoperative pulmonary hypertension depends upon several factors including the patient's age and diagnosis and cardiorespiratory function. Various pathophysiologic factors affect pulmonary vascular resistance. Intensivists should seriously consider and manipulate these factors to control pulmonary artery pressure and prevent a hypertensive crisis.

Increasing the depth of analgesia and sedation, especially before invasive procedures, is an important strategy to reduce pulmonary vascular resistance. As the decreased PaO_2 and increased $PaCO_2$ can constrict the pulmonary arteries, a ventilator should be set up to achieve $PaO_2 > 100$ mmHg and $PaCO_2$ at 30–35 mmHg. Acidosis stimulates pulmonary hypertension, so PH should be kept at least 7.40 (Rudolph and Yuan 1966; Hoffman et al. 1981).

Regarding mechanical ventilation, either hypo- or hyperinflation of the lungs should be avoided. Intrathoracic pressure should be kept as low as possible. Parenchymal lung abnormalities, like pneumonia and atelectasis, can also increase pulmonary arterial pressure. It is important to pay attention to chest radiographs and physical examination findings to detect and treat these problems.

Many of the inotropic drugs used after cardiac surgery have nonspecific vasoconstrictive effects when prescribed in high doses, so dose reduction of these drugs should be considered as a strategy to lower pulmonary vascular resistance. On the other hand, there are intravenous vasodilators that can treat pulmonary hypertension by different mechanisms. Nitric oxide donors like nitroprusside, milrinone, eicosanoid prostaglandins, the gas nitric oxide, magnesium, isoproterenol, and dobutamine are among them. All of the above-mentioned vasodilators, except for the nitric oxide, have nonspecific vasodilation so systemic hypotension as a side effect can limit their usage (Atz and Wessel 1997). In chronic management, oral treatment with phosphodiesterase inhibitors (sildenafil) and endothelin receptor blocking agents (bosentan) is usually prescribed. The interested reader is addressed to chapter "Pulmonary Hypertension in Congenital Heart Diseases".

Conclusion

The improved results of cardiac surgery for congenital heart disease are attributed to the high quality of postoperative care in recent years. It is important to observe patients closely by repeated physical examination and to be vigilant for early signs of complications because anticipatory rather than reactive care leads to acceptable postoperative outcomes.

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Postoperative Arrhythmias and Their Management

Majid Haghjoo and Mohammadrafie Khorgami

Abstract

Early cardiac arrhythmias are well-known complications of pediatric cardiac surgery. These arrhythmias are also a major cause of mortality and morbidity. Several reports have been published regarding late postoperative arrhythmias after pediatric cardiac surgeries. Nevertheless, data related to the early postoperative period after cardiac surgery in children are limited. Arrhythmias that may be easily tolerated in normal heart can have a major influence on hearts with congenital defects. Postoperative cardiac arrhythmias range from simple atrial or ventricular ectopies to major arrhythmias such as atrial flutter/fibrillation or ventricular tachycardia. Other common arrhythmias are junctional ectopic tachycardia or complete atrioventricular block after any manipulation on conduction system. Several factors, including myocardial dysfunction, electrolyte disturbances, adrenergic stimulation, sutures in the myocardium, residual hemodynamic impairment, as well as pain and anxiety, have been implicated in pathogenesis of early postoperative arrhythmias in children. The aim of this chapter is to present an overview of the common cardiac arrhythmias occurring in immediate postoperative period.

Keywords

Pediatric · Cardiac surgery · Postoperative Arrhythmia · Management · Atrial fibrillation Bradycardia · Ventricular tachycardia Ventricular fibrillation

Early cardiac arrhythmias are well-known complications of pediatric cardiac surgery. Available data show an incidence of 27–48% (Rekawek et al. 2007). In early postoperative period of cardiac operations, arrhythmias are also a major cause of mortality and morbidity. Several reports have been published regarding late postoperative arrhythmias after cardiac surgeries such as the Mustard or Senning operation and Fontan procedures (Weber et al. 1989). Nevertheless, data related to the early postoperative period after cardiac surgery in children are limited. Arrhythmias that may be easily tolerated in normal heart can have a major influence on hearts with congenital defects (Triedman 2002).

Postoperative cardiac arrhythmias range from simple atrial or ventricular ectopies to major arrhythmias such as atrial flutter/fibrillation after Mustard/Senning or ventricular tachycardia after repair of tetralogy of Fallot. Other common arrhythmias are junctional ectopic tachycardia

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(JET) after repair of ventricular septal defect (VSD) or complete atrioventricular block (CHB) after any manipulation on conduction system (Delaney et al. 2006).

Several factors, including myocardial dysfunction, electrolyte disturbances, adrenergic stimulation, sutures in the myocardium, residual hemodynamic impairment, as well as pain and anxiety, have been implicated in pathogenesis of early postoperative arrhythmias in children. The aim of this chapter is to present an overview of the common cardiac arrhythmias occurring in immediate postoperative period.

Postoperative Tachyarrhythmias

Postoperative tachycardias may be of atrial, junctional, or ventricular origins. The cause of these tachycardias is procedure-related injuries to the atria, conduction system, or ventricles and may be perpetuated by intraoperative myocardium ischemic injury, electrolyte disturbance, catecholamine stimulation, and hemodynamic disturbances. Supraventricular tachycardia is defined as arrhythmia originating from atria, atrioventricular node, and His bundle, whereas ventricular tachycardia originates from the structures located below His bundle including bundle branches, Purkinje system, and ventricular myocytes.

Supraventricular Tachycardias

In evaluation of postoperative supraventricular tachycardia, we should first determine the mechanism of arrhythmia. Automatic tachycardias are the most common postoperative supraventricular tachycardias. Reentrant tachycardias are observed with lower frequency in early postoperative period.

Junctional Ectopic Tachycardia

Junctional ectopic tachycardia (JET) is the most common postoperative tachycardia in pediatric population (Zampi et al. 2012). The incidence of postoperative JET estimated to be between 3.6% and 10% after repair of congenital heart defects and in some studies reported up to 27% (Batra et al. 2006; Dodge-Khatami et al. 2002; Hoffman et al. 2002; Mildh and Hiippala 2011; Yildirim et al. 2008). This tachycardia is more common in infants. This tachycardia is characterized by ventricular rate of 140–220 bpm, atrioventricular (AV) dissociation, and less commonly 1:1 ventriculoatrial (VA) conduction (Fig. 1).

Although majority of the postoperative JET spontaneously resolves after a few days, period of sustained arrhythmia has devastating effect on the hemodynamic states and should be treated immediately and appropriately. At first step, the predisposing factors should be eliminated. These measures included body surface cooling to 34 to 35 °C, elimination of inotropes, correction of electrolytes abnormalities, and stabilization of hemodynamic condition (Lan et al. 2003). If the arrhythmias do not respond to these therapies, anti-arrhythmic drug is indicated and most experts begin with intravenous amiodarone. Compared with pre-amiodarone era, this drug markedly reduced postoperative mortality related to JET from 35% to 4% (Probst et al. 2007). The conversion to sinus rhythm may not be possible in all patients with amiodarone; however, reducing the ventricular rate would be acceptable in these patients. Amiodarone is initiated with loading dose of 5 mg/kg intravenously during 1 h and then continued with infusion of 10–15 μg/kg/min (Perry et al. 1996; Kovacikova et al. 2009). Oral therapy should be started one to two days before discontinuation of IV therapy. If the arrhythmia was refractory to amiodarone, betablocker, digoxin, or flecainide can be added to amiodarone regimen. Catheter ablation is rarely indicated in drug-refractory patients.

Atrial Tachycardia

Focal atrial tachycardia (AT) is the second postoperative tachycardia with automatic mechanism. This tachycardia is described as a narrow QRS tachycardia, ventricular rate of 150–250 bpm,

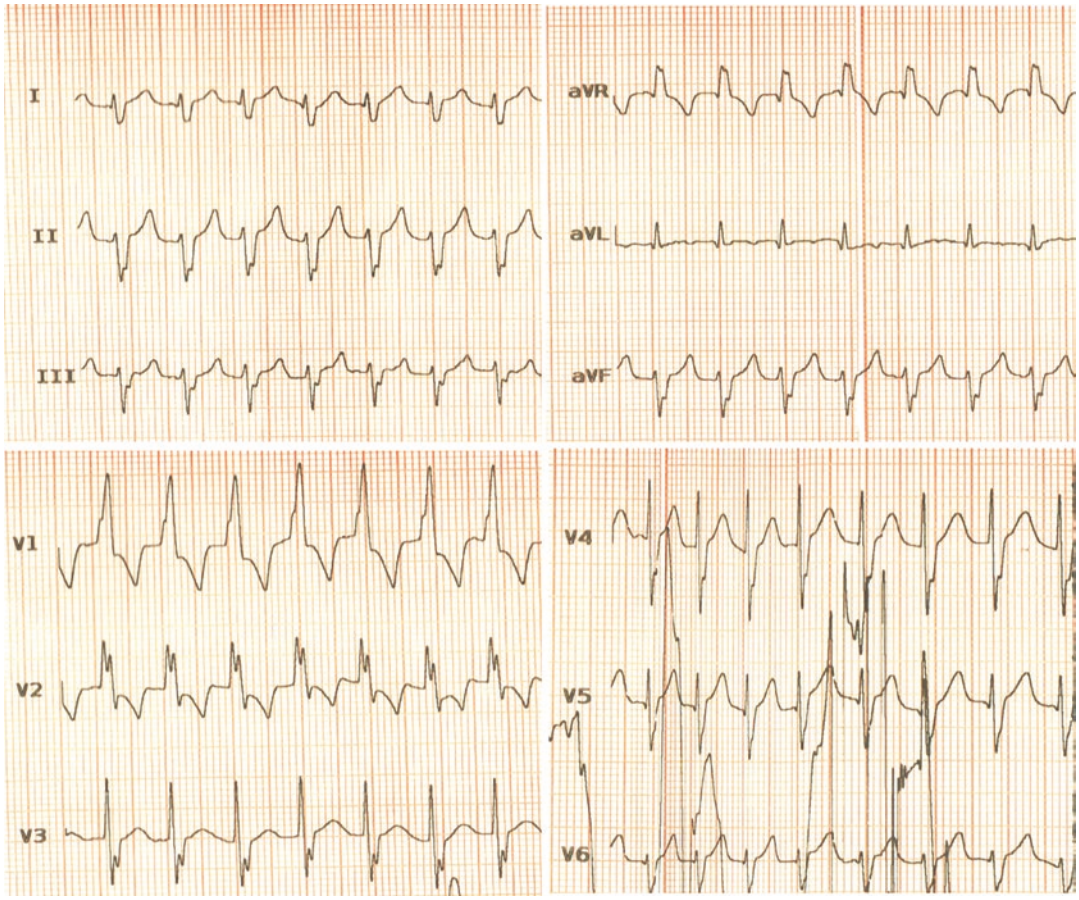

Fig. 1 Junctional ectopic tachycardia after complete atrioventricular septal defect repair. This ECG shows regular tachycardia with 1:1 ventriculoatrial conduction and right bundle branch block type morphology

warm up/cool down behavior, and variable atrial rate because of autonomic fluctuation (Walsh et al. 1992) (Fig. 2). Injury to atrial myocardium is one of the main pathologic factors. Vena caval cannulation during cardiac surgery and CV line insertion are other predisposing factors. Sinus node dysfunction is also a risk factor for AT. Automatic AT should be treated similar to JET.

Atrial flutter (AFL) and intra-atrial reentrant tachycardia (IART) are atrial arrhythmias with reentrant mechanism. These arrhythmias are recognized on an ECG in the presence of narrow QRS tachycardias and characteristic "saw-tooth" wave in AFL or "isoelectric line" in IART at a regular rate of 240–440 bpm (Fig. 3). Ventricular rate depends on status of AV node (Fig. 4). Many factors predispose patients to AFL/IART. The most important factor is the degree of injury to atrial myocardium and region of scars and fibrotic tissue after atriotomy, incision, and suture lines. Other causes include the presence of atrial enlargement due to preexisting valvular disease and hemodynamic instability. Treatment should be focused on elimination of predisposing factors, rectification of residual defect as much as possible, and improvement of hemodynamic status. If the AFL and IAART are associated with acute hemodynamic instability, synchronized electrical cardioversion of 0.5–1 J/kg should be

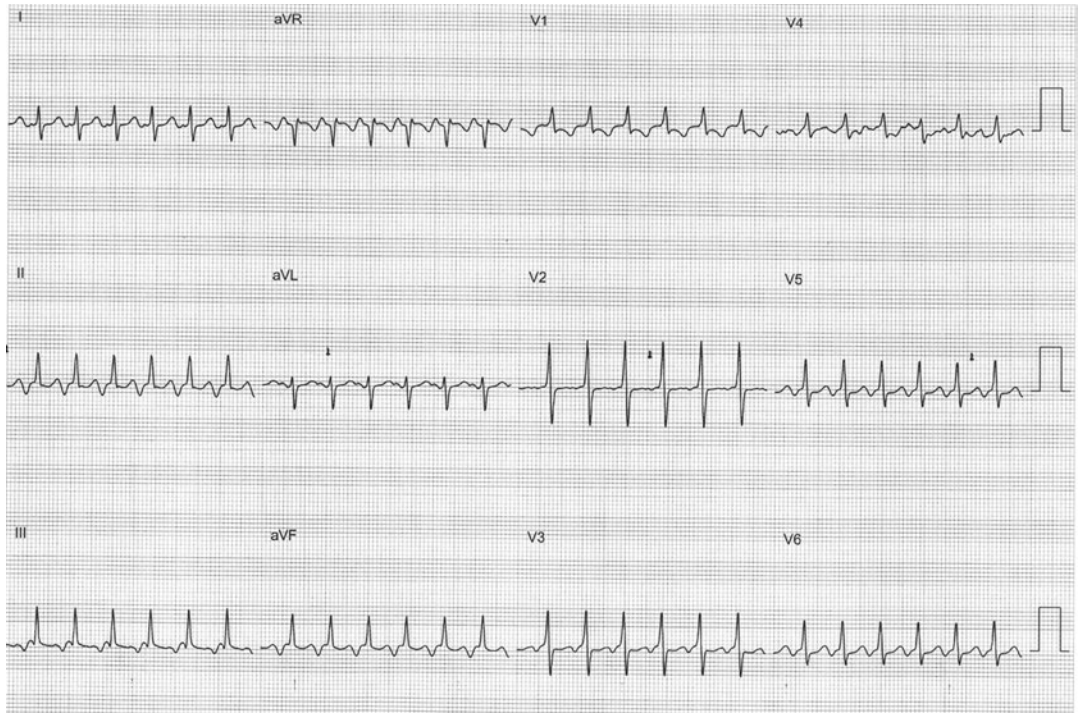

Fig. 2 Atrial tachycardia after Ebstein anomaly repair. Note that there is regular narrow QRS tachycardia with short PR and long RP interval, negative P waves in inferior leads, and positive P waves in leads I and aVL

done immediately. Success rate of cardioversion is reported up to 87% (Texter et al. 2006). Antiarrhythmic drug therapy is indicated if the arrhythmia persists. Class IC antiarrhythmic drugs such as flecainide or propafenone is recommended for rhythm control in setting of preserved left ventricular function; however, amiodarone is the first choice drug in patients with reduced left ventricular function. Because of high incidence of amiodarone-related complications, careful patient follow-up is necessary. These assessments included ECG, chest X-ray, spirometry, and appropriate laboratory test including thyroid and liver function tests. If the rate control is planned, beta-blocker is the first line of therapy. Propranolol is usually well tolerated in children. In emergency setting, esmolol infusion with blood pressure monitoring is necessary. Most experts recommended combination of class IC drugs with beta-blocker for prevention of 1:1 AV conduction after atrial rate reduction by class IC drugs. In drug-refractory patients, catheter ablation is recommended. The arrhythmia circuit is usually located in scar regions and cannulation area.

AV Nodal Reentrant Tachycardia and AV Reciprocating Tachycardia

AV reciprocating tachycardia and AV nodal reentrant tachycardia with reentrant mechanism are less common arrhythmia after cardiac operation. These arrhythmias are regular narrow QRS tachycardias with heart rate of 150–250 bpm, paroxysmal initiation and termination, and P-wave deflection at end of QRS or in the ST segment (Fig. 5). These arrhythmias may be controlled with vagal maneuvers but usually easily respond to intravenous adenosine. Treatment of underlying causes such as premature beats as a trigger, myocardial stress, and electrolyte disturbance has a critical role (Huang and Wood 2006).

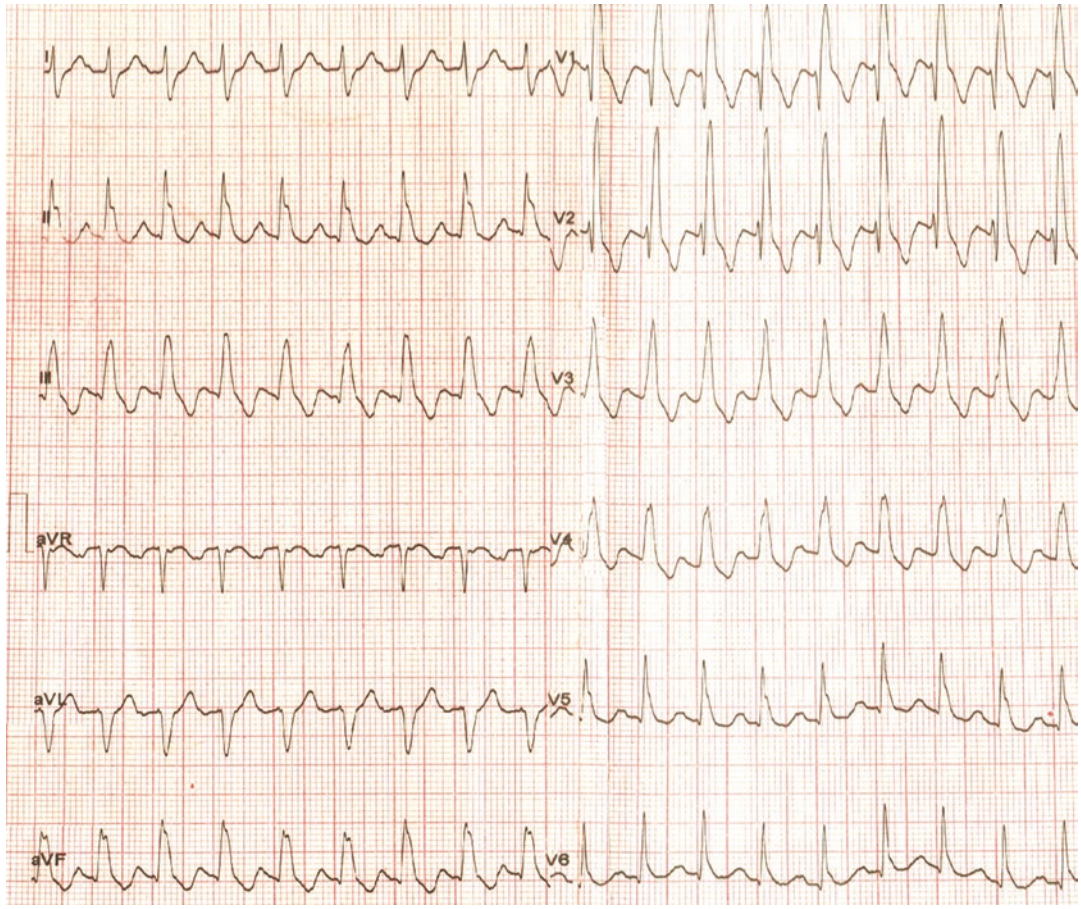

Fig. 3 Atrial flutter after atrial septal defect repair. This ECG shows regular wide QRS tachycardia with ventricular rate 150 beats/min and typical "saw-tooth" pattern (arrows)

Ventricular Tachycardias

Ventricular arrhythmia has been reported in 1–5% of pediatric patients who have had palliative surgery for congenital heart disease; however, in Hoffman et al. study incidence of nonsustained VT was 15.2% (Delaney et al. 2006). VT refers to wide QRS tachycardia with heart rate ≥100 bpm, VA dissociation, and sometimes 1:1 VA conduction (Fig. 6). The SVT with aberrancy and antidromic AVRT also stay on the list of differential diagnosis of wide complex tachycardia. However, postoperative wide QRS tachycardia should be considered VT until proven otherwise.

Perioperative ischemic-reperfusion events after cardiopulmonary bypass with damage to myocardium are main predisposing factors. Measurement of myocardial biomarkers such as troponin I may be useful (Delaney et al. 2006; Pfammatter et al. 2002). Hypercatecholaminergic state, inotropes, electrolyte, and metabolic abnormalities may also predispose the pediatric patients to ventricular arrhythmias in early postoperative period (Peretto et al. 2014). Scar-related ventricular arrhythmia usually presents a monomorphic VT. This kind of arrhythmia has been observed both early and late after pediatric cardiac surgery. Some types of CHD-like tetralogy of Fallot are more susceptible to this arrhyth-

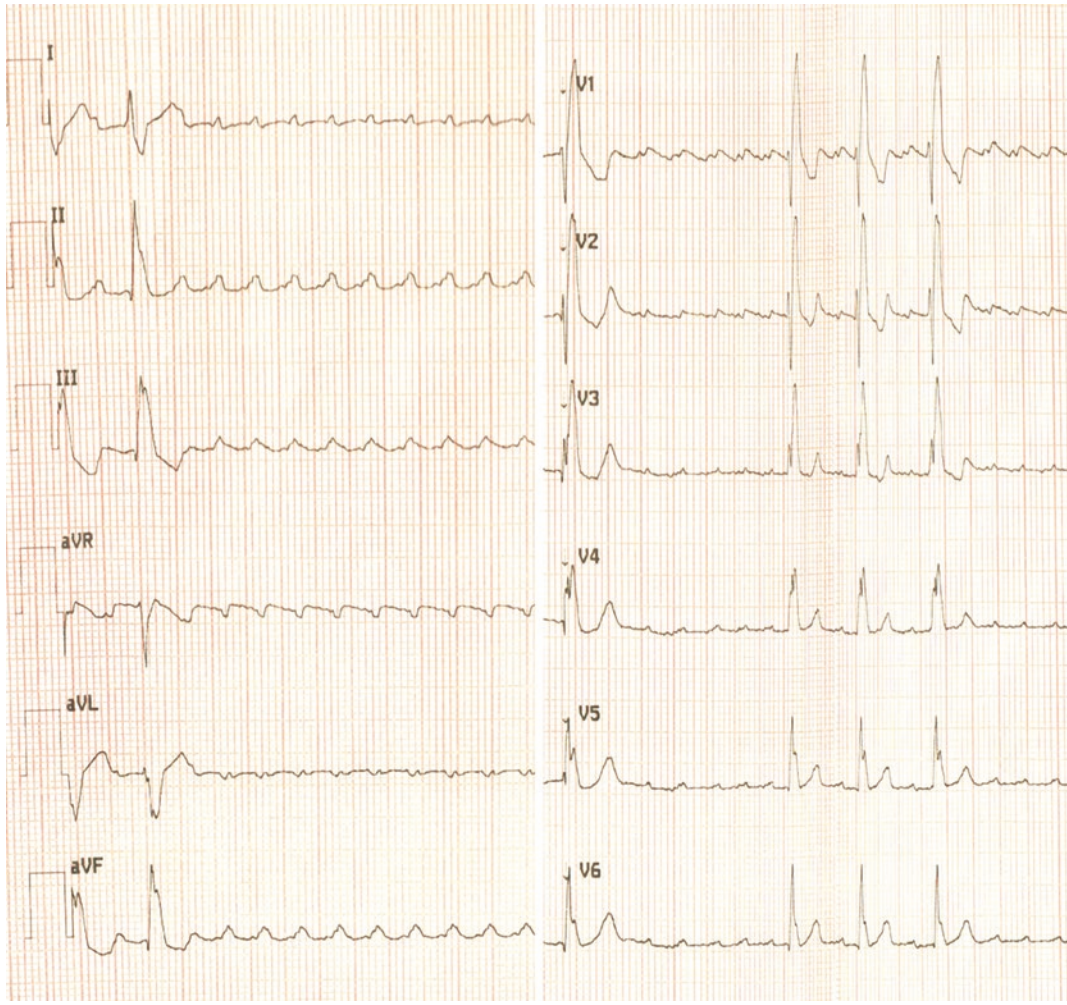

Fig. 4 Atrial flutter after adenosine injection. Typical "saw-tooth" pattern is now clearly seen after adenosine-induced atrioventricular block

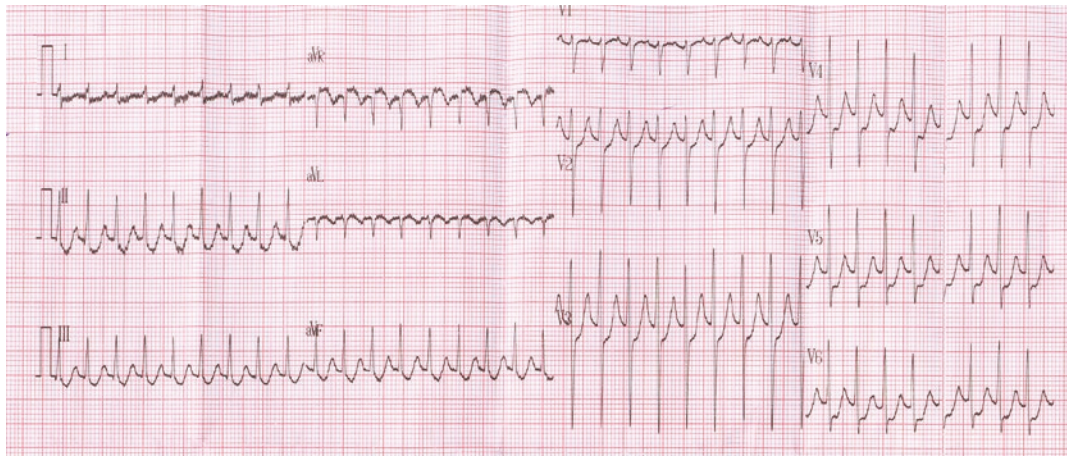

Fig. 5 Orthodromic atrioventricular tachycardia. Characteristic features are ST-segment depression in inferior and left precordial leads and ST-segment elevation in lead aVR

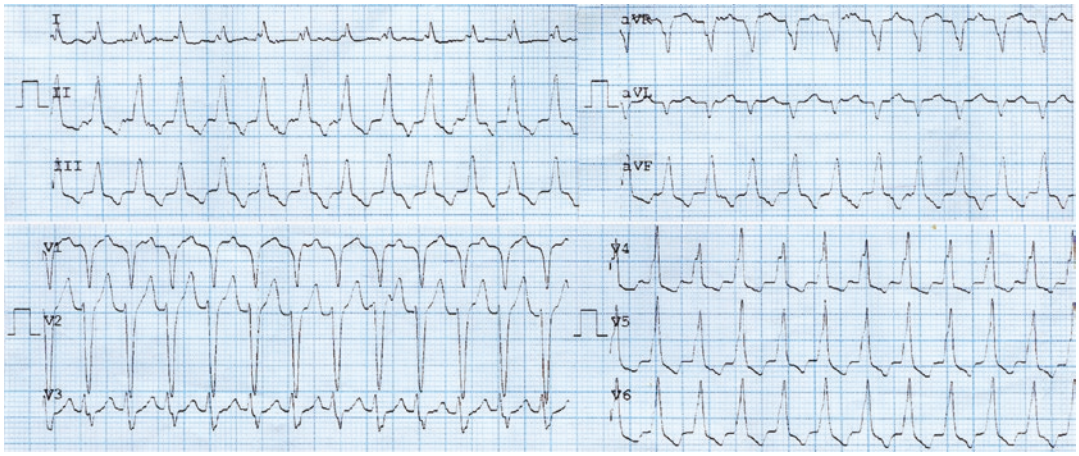

Fig. 6 Ventricular tachycardia after tetralogy of Fallot repair. There is atrioventricular dissociation (arrows), inferior axis, and left bundle branch block type morphology (right ventricular outflow tract origin)

mia (Huehnergarth et al. 2008). The incidence of scar-related arrhythmia gradually increased with time and degree of damage to myocardium, and the extent of scar determines arrhythmia character and frequency (Zeppenfeld et al. 2007; Papagiannis 2005). Basically, all postoperative events that terminated to low cardiac output and decreased ventricular function could cause ventricular arrhythmia that itself could deteriorate the cardiac output that worsen the patient hemodynamic condition.

In most patients, postoperative premature ventricular complexes resolved spontaneously without serious complication. If the patient developed hemodynamically unstable VTs, immediate electrical cardioversion of 1–2 J/kg is indicated (Kleinman et al. 2010). In patients with stable sustained VT, intravenous amiodarone is the first line therapy.

Postoperative Bradyarrhythmias

Sinus Node Dysfunction

Although sinus node dysfunction (SND) has been reported rarely in children with normal heart, it has been recognized with higher frequency in children with CHD especially after cardiac repair. SND may occur in the form of sinus arrest, sinoatrial exit block, marked sinus bradycardia, or brady-tachy syndrome. Majority of SNDs are consequence of procedures associated with atrial tissue damage such as Mustard or Senning operation, Fontan procedure (Fig. 7), secundum ASD closure, and endocardial cushion defect repair (Walsh and Cecchin 2007). Only symptomatic patients require permanent pacing.

Atrioventricular Block

Despite the major progress in CHD management, atrioventricular block (AVB) continues to complicate 1–3% of surgical repairs (Bonatti et al. 1998; Weindling et al. 1998). CHB is the most common type of conduction disturbance after CHD repair; however, second-degree and first-degree AVB may also occur. Most of postoperative CHBs are related to procedures involving the VSD closure; they usually occur early in the postoperative period; in few cases, they also may occur several months or years after surgery. Early postoperative AVB can be temporary or permanent. Permanent pacing is not indicated in the former. In contrast, permanent pacing is necessary if second- or third-degree AVB persists at least one week after surgery, because the block is usually related to His bundle or trifascicular damage, and this can be associated with risk of asystole and sudden cardiac death (Brugada et al. 2013). In patients

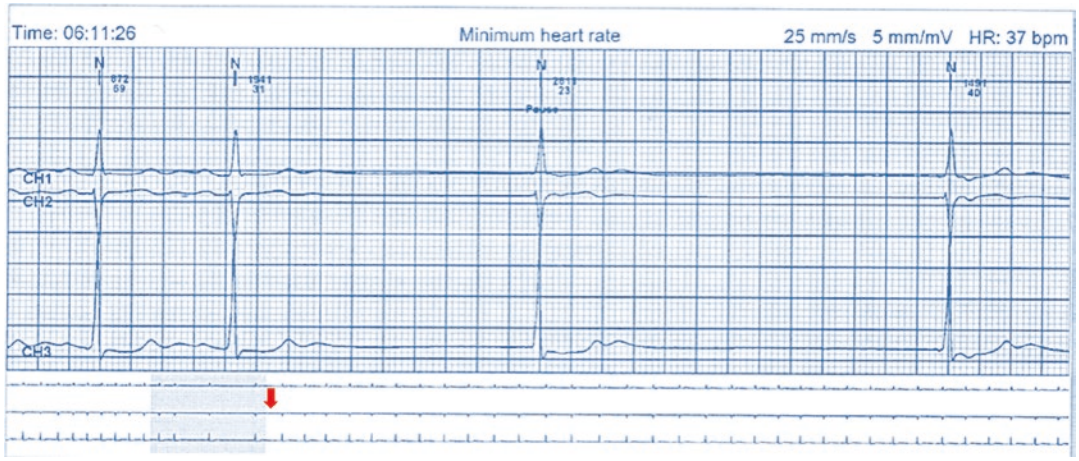

Fig. 7 Sinus node dysfunction after Fontan operation. Ambulatory ECG monitoring in a 5-year-old girl after Fontan surgery showed sudden onset sinus arrest with two junctional escape beats and then return of normal sinus rhythm (red arrow)

who have temporary pacemaker (TPM), it is crucial to have continuous monitoring for early detection of TPM malfunction.

Common Surgical Procedures Associated with Postoperative Arrhythmias

Atrial Septal Defect Closure

Supraventricular tachycardia are the most common arrhythmias after ASD surgical closure. The SA node dysfunction may also be observed due to surgical manipulation in right atrium. Early postoperative arrhythmias are usually well tolerated because isolated ASDs have benign course if treated in appropriate time and do not affect the cardiac reserve. Venous cannulations have a role in early arrhythmia, and modification of surgical procedure decreased the incidence of arrhythmia (Bink-Boelkens et al. 1988).

In most studies, main factor determining late postoperative arrhythmia is patient age at the time of ASD closure (Roos-Hesselinka et al. 2003; Murphy et al. 1990). Other important factor is the period of follow up; an increased prevalence of arrhythmia was observed over the time. Patients with preoperative arrhythmia and sinus node disease have a greater chance for continuation of arrhythmia after surgery (Karpawich et al. 1965).

Ventricular Septal Defect Closure

VSD closure is the most common CHD surgical repair in pediatric group (Hoffman and Kaplan 2002). VSD type and location are the main factors in predicting conduction disorder and arrhythmia after surgery (Fig. 8). Most of the VSDs are located in perimembranous area and less commonly in the muscular area. Understanding the anatomic course of conduction system and its relation with VSD is very important in avoiding injury to these structures. AV conduction system descends in posteroinferior rim of perimembranous VSD and left ventricular outflow tract; therefore, this area is very susceptible to injury during surgical repair. In contrast to perimembranous VSD, AV conduction system runs at anterosuperior rim in inlet VSD, and the risk of surgical damage is lower (Ho and Anderson 1985). In earlier reports, the incidence of AV block was as high as 25%. Better knowledge of the AV conduction axis in different forms of CHD and improved surgical techniques decreased this risk to 1% after perimembranous VSD closure (Andersen et al. 2006). Other important risk fac-

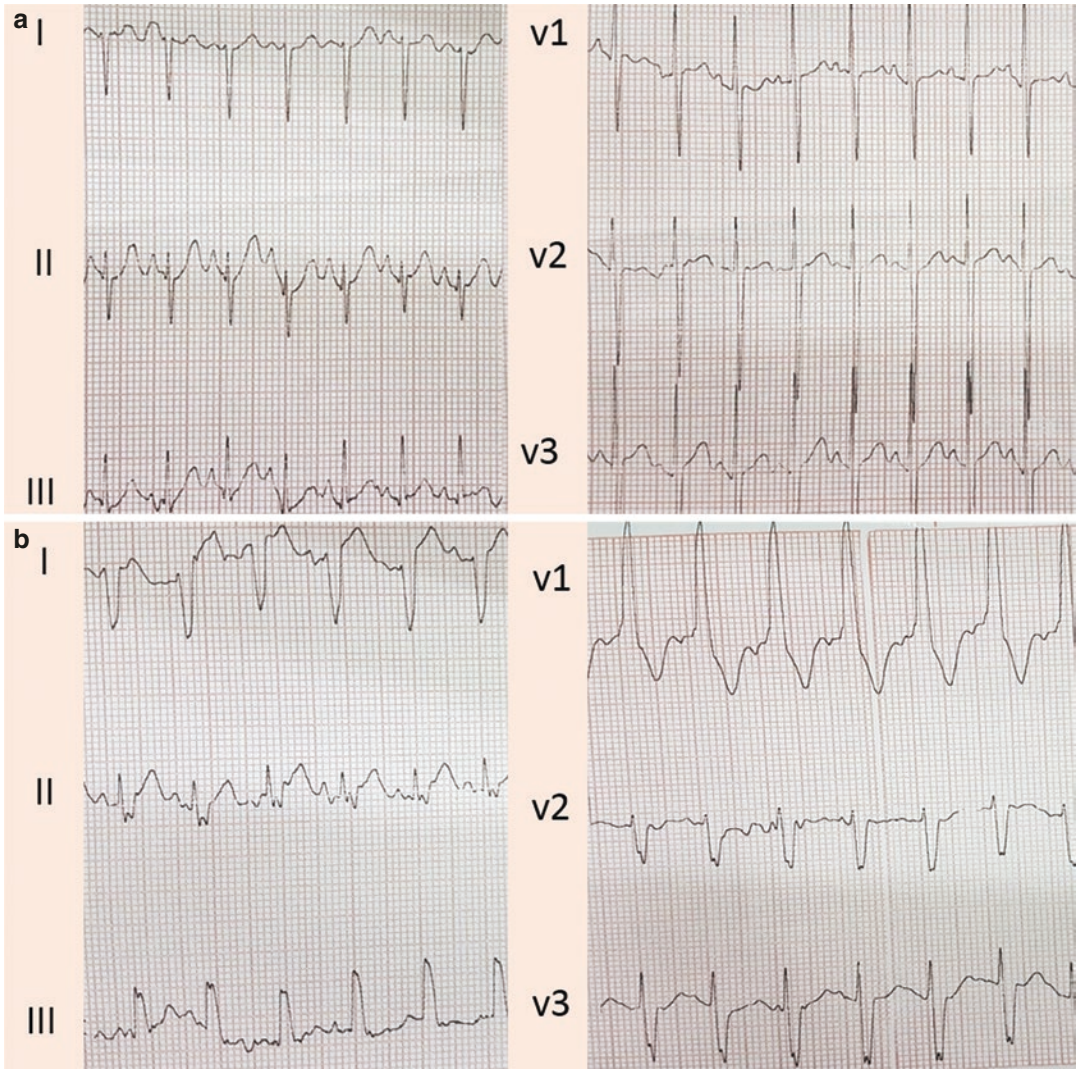

Fig. 8 Postoperative changes in ECG after surgical VSD repair. (**a**) ECG before surgery. (**b**) ECG after surgery in same patient showed new right bundle branch block

tors are Down syndrome, lower body weight, younger ager, longer cardiopulmonary bypass time, higher surgical complexity, and residual defect (Tucker et al. 2007). The technique of repair has also a clear effect on postoperative arrhythmia; the prevalence of RBBB and ventricular arrhythmias are higher in ventriculotomy approach than atriotomy (Houyel et al. 1990).

If third or high grade, AV block persists more than 7–10 days after operation, permanent pacemaker is indicated (Brugada et al. 2013). Resolution of AV block has been observed in 9.6% of the patients after permanent pacemaker implantation, but extraction of pacemaker in these patients is a controversial issue (Batra et al. 2003). Sinus node dysfunction may also be observed due to venous cannulation. According to the guidelines, symptomatic SND may need pacemaker implantation (Roos-Hesselinka et al. 2006).

Atrioventricular Septal Defect Repair

Atrioventricular septal defects (AVSD) is an endocardial cushion defect that consists of a combination of ASD, VSD, and AV valve anomalies. There are two types of this anomaly: partial AVSD and complete AVSD.

Complexity of this defect makes complete surgical correction somewhat challenging. In this lesion, AV node shifted posteroinferiorly; therefore, it may be damaged during repair. CHB is uncommon after partial AV canal repair, but complete AVSD is one of the most common settings for CHB after surgical repair. Younger age at operation, lower weight, and prolonged aortic cross clump are risk factors for CHB. Remaining residual septal defect and AV valve regurgitation predisposed patients to late post-operative arrhythmia.

Supraventricular tachyarrhythmias have been reported in 11.3% after surgery (Chowdhury et al. 2009). Various forms of SVT including atrial flutter, atrial fibrillation, and focal atrial tachycardia were observed after surgical repair. The residual left-to-right shunts and AV valve regurgitation that usually progress with time and persistent of pulmonary hypertension are the risk factors for late postoperative SVT. The increased age at operation is another risk factor for SVT.

Tetralogy of Fallot Correction

The TOF correction includes VSD closure and repair of RVOT stenosis with shaving, transannular patch, conduit, and homograft. Multiple factors are responsible for susceptibility to postoperative arrhythmias; right ventriculotomy, ventricular fibrosis, RV pressure/volume overload due to residual defects, such as residual VSD, and pulmonary stenosis/regurgitation all are risk factors for developing ventricular. In addition, LV dysfunction, ventricular interaction, and mechanical dyssynchrony have a role in genesis of postoperative arrhythmias (Walsh and Cecchin 2007).

Injury to conduction system during surgical repair results to RBBB in more than 90% of patients. Pulmonary regurgitation effects on the PR interval and QRS duration and prolongation of these variables with time have prognostic value for the late postoperative arrhythmia.

In the study of Gatzoulis et al. (Gatzoulis et al. 1995), QRS duration ≥180 ms and prolongation of QRS > 5 ms/year over a 10-year period were predictors for ventricular tachycardia and late sudden death. Appropriate timing of TOF surgical correction and pulmonary valve replacement could significantly decrease the risk of ventricular arrhythmia in these patients. Late SCD is the well-recognized complication of TOF surgical correction. This complication has been reported in up to 4.6% of patients. SCD is mainly related to ventricular arrhythmias and less commonly CHB (Chandar et al. 1990). To determine the risk of ventricular arrhythmia and SCD after surgical correction, a combination of various diagnostic modalities is necessary. These modalities include 24-h ambulatory ECG monitoring, exercise test, electrophysiologic study, signal averaging, echocardiography, and MRI (Steeds and Oakley 2004).

Ambulatory ECG monitoring is useful for evaluating PVCs count and morphology. After TOF surgical correction, frequent PVCs have been reported in 20–40% patients (Zimmermann et al. 1991; Kavey et al. 1982; Deanfield et al. 1984). Patient with PVCs and VT on resting ECG may benefit from exercise test (Garson et al. 1980). If PVCs and VT are still inducible during exercise test, patient has a significant cardiac dysfunction and may be at the risk of SCD. Suppression of PVCs during exercise testing may be associated with better prognosis, but PVC suppression does not necessarily indicate a benign prognosis.

The role of electrophysiologic study in predicting high-risk patient for sudden death still remained controversial. Chander et al. (Chandar et al. 1990) reported that induction of sustained and nonsustained VT at EPS correlated with PVCs on ambulatory ECG monitoring and occurrence of syncope during follow-up. Two factors that associated with VT inducibility are older age at the time of repair and longer follow-up period after surgery (Dunnigan et al. 1984). Zimmermann et al. (Zimmermann et al. 1991) evaluated some

variables that participate in ventricular arrhythmia after TOF repair. Thirty-two percent of the patients have late potentials. These patients are more likely to have inducible VT during EPS. The incidence of inducible VT during EPS in asymptomatic patients was 10% in this study.

Surgical Repair of Univentricular Heart

Fontan procedure is a surgical technique in which blood from systemic venous return could access directly to pulmonary artery and bypass the heart. This procedure was done in congenital heart disease in which subpulmonic ventricle or right heart is not properly formed. This surgical approach is done commonly in tricuspid atresia and pulmonary atresia. In classic Fontan, SVC is anastomosed to right pulmonary artery and left atrial appendage to left pulmonary artery. As a result, right atrium is part of blood transmission pathway. There are two modifications of the original operation that are most widely used today. In the *lateral atrial tunnel Fontan*, a baffle is placed in the right atrium to partition systemic from pulmonary venous blood, and in the *extracardiac conduit Fontan*, one end of a synthetic tube graft is connected to the inferior vena cava and the other end to the pulmonary artery confluence. Pressure and volume overload in the atria gradually provides necessary substrates for atrial arrhythmias and sinus node dysfunction. In addition, extensive atriotomy, suture lines, and injury to SA node and its blood supply are other important risk factors.

The postoperative arrhythmias have been reported in 14–50% (Weber et al. 1989; Porter et al. 1986; Girod et al. 1987). Atrial tachycardia is the most common arrhythmia after Fontan operation. Other arrhythmias such as JET and VT are observed less frequently. In Gelatt study (Gelatt et al. 1994), early atrial tachycardia after Fontan surgery was observed in 20% of patients. This arrhythmia in addition to atriopulmonary connection and longer follow-up are independent risk factors for late arrhythmia. Loss of the sinus node dysfunction occurred in more than 50% of patients during 10-year follow-up after Fontan procedure. Electrophysiologic study revealed abnormal sinus node dysfunction and intracardiac conduction delay in 60% patients (Kurer et al. 1991). Bradyarrhythmias are usually better tolerated than tachyarrhythmia; however, SND predisposed patients to tachycardia–bradycardia syndrome. Similar to the tachyarrhythmias, early postoperative bradyarrhythmias are the predictors for late bradyarrhythmias. It appears that incidence of early and late arrhythmias and SND is lower in *extracardiac conduit Fontan* compared with other surgical modalities (Nürnberg et al. 2004; Quinton et al. 2015).

Surgical Correction of Transposition of the Great Arteries

In transposition of great arteries (TGA), left ventricle that received pulmonary venous return from LA is connected to pulmonary artery, and right ventricle that received venous return from RA is connected to aorta. As a result, in case of inadequate mixing of right and left heart blood, severe cyanosis occurs.

Corrective surgeries include physiologic correction or atrial switch (Mustard and Senning operation) and anatomic repair or arterial switch. Anatomic LA is connected to subaortic ventricle (morphological RV) using pericardial tissue in Mustard operation and using atrial baffle in Senning operation. Also, RA (received venous return) connected to subpulmonic ventricle (morphological LV). Redirecting systemic and pulmonary venous circulations in atrial switch is associated with extensive atriotomy and resultant injury to the SA node with subsequent risk of atrial tachyarrhythmia and SND.

Atrial flutter and ectopic atrial tachycardia are well-recognized arrhythmia after Mustard and Senning operation. The rate of these arrhythmias increased progressively with time along with loss of sinus rhythm and SA node function (Gillette et al. 1974; Khairy et al. 2004; Moons et al. 2004). Gelatt et al. (1997) reported sinus rhythm in 77% patients in first 5-year after operation that decreased to 40% after 20 years. Predisposing

factors were previous septectomy, postoperative bradycardia, and late atrial flutter, such as in Fontan operation, early postoperative arrhythmia is the risk factor for late arrhythmia and death. Anti-arrhythmic drugs are usually not effective in these patients. Pacemaker therapy is other treatment option for brady-tachy syndrome, syncope, symptomatic bradycardia, ventricular dysfunction with bradycardia.

Arterial switch operation is associated with lesser manipulation of intracardiac structures. Therefore, atrial rhythm disturbance and arrhythmia are less common compared with atrial switch repair. Actually, corrected sinus node recovery times are normal in most patients. Furthermore, AH and HV intervals are preserved in most cases. In arterial switch, damage to AV node is uncommon and second- or third-degree AV blocks are limited to cases with VSD closure. RBBB is more common in TGA/VSD repair but also observed in TGA/IVS. Other complications after arterial switch are ventricular and atrial ectopies. Rhodes (Rhodes et al. 1995) reported PVCs in 70% of patients in ambulatory ECG monitoring after operation that decreased to 30% in mean 2.4-year follow-up. Obstruction of coronary artery during surgical anastomosis may result in myocardium ischemia/infarction and predisposed patients to ischemic ventricular arrhythmia. These patients may be asymptomatic, and the presence of ventricular arrhythmia after arterial switch operation should arise suspicious to coronary arteries obstruction (Mayer Jr et al. 1990).

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Postoperative Respiratory Management in Pediatric Cardiac Surgical Patients

Ali Dabbagh

Abstract

Any respiratory disorder, even the mild forms, could affect the health state of any human being. This is why respiratory care is considered an ingredient part of care in every patient, and this is undoubtedly much more important in patients with congenital heart disease. In this chapter, the principles of respiratory care in the postoperative period in congenital heart disease patients are discussed with the following subtitles: "How does the pediatric patient differ from the adult patient?," "Principles and Goals of mechanical ventilation in the postoperative period," "Ventilation considerations specific for congenital heart patient," Strategies for ventilation and ventilator modes," "Readiness for extubation and extubation failure," "Non-invasive ventilation, i.e. NIPPV—RAM cannula, nCPAP, High flow nasal cannula, etc.," and "Miscellaneous issues, including Extra-corporeal CO_2 removal (ECCO2R), High-frequency oscillatory ventilation (HFOV), Inhalational routes of drug delivery, Chest physiotherapy, Chronic respiratory failure, and tracheostomy."

Keywords

Respiratory care · Congenital heart disease
Postoperative care · Noninvasive ventilation
Chest physiotherapy · Extubation
Tracheostomy

How Does the Pediatric Patient Differ from the Adult Patient?

There are several main anatomic and physiologic differences between adults and pediatric patients concerning airway and ventilation. These changes are most significant during the neonatal period up until 1 year of age. Based on a long list of studies, the major differences between the anatomy and physiology of the respiratory system between pediatric and adult patients could be described as the following anatomical and physiological features (Dickison 1987; Commare et al. 1994; Tripp and Bolton 1998; Adewale 2009; Walker and Ellwood 2009; Baker and Parico 2010; Ahmadpour-Kacho et al. 2011; Heinrich et al. 2012; Sunder et al. 2012; Harless et al. 2014; Saikia and Mahanta 2019; Vijayasekaran 2020; Isa et al. 2021; Chuang et al. 2022; Dariya et al. 2022):

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Anatomical Features

- The **occiput** is protruding and the **head** is large enough to induce head flexion and major impediments in the alignment of the airway for intubation,
- The **tongue** is larger compared with adults,
- Generally, the **airway** is smaller with a very small opening,
- More **cephalic location** of the airway located at the level of the third and fourth cervical spines (C3 & C4). However, the airway moves more caudally as the child grows up, mainly as a result of cervical spine growth,
- The pediatric airway is **loose** compared with adults (less cartilaginous tissue),
- The **epiglottis** is more edematous and floppy ("U" shaped feature),
- Vocal cords do not conform to a right angle with the larynx; instead, they have an anterior-inferior to posterior-superior angled fashion,
- Maybe the most practical point is that the **narrowest point** in the pediatric airway is located distal to the vocal cords; while in adults, the vocal cords are the narrowest part of the airway. The shape of the larynx in pediatric patients is **funnel-shaped** while the larynx in adults is tunnel-shaped,
- The **trachea** is smaller and shorter, increasing the chance for one-lung intubation with the least neck movements,
- Adult difficult airway algorithms do not necessarily work for children and neonates and pediatric difficult airway algorithms should be always available.

Physiological Features

There are several physiologic differences between adult and pediatric patients which include the following

- The lung volume compared to weight is much smaller in children and neonates,
- The airway cross-sectional area is smaller creating higher resistance to airway,
- **Nasal ventilation** is the main route of ventilation, especially in neonates,
- **Functional residual capacity** (FRC) compared to weight is less than adults leading to smaller reserve volumes; oxygen saturation decompensates much earlier during respiratory distress or induction of anesthesia or sedation for intubation,
- **Less cartilaginous structure** of the upper airway components and large lower airways leads to dynamic airway compression during forceful ventilation which is an early component of respiratory distress; since it induces more negative inspiratory pressure and more respiratory distress, which in turn leads to aggravated ventilation; this process, in a vicious cycle, leads to more and more respiratory distress,
- The smaller size of the **lower airways** leads to a much more severe decrease in the total area of the airway due to presumed airway edema compared to adults,
- The **main respiratory muscle** in neonates and adults is the **diaphragm**. Accessory muscles are neither efficient nor do they play a significant role in respiration. If diaphragm failure is present (i.e., due to paralysis of the vagus nerve), postoperative ventilation would be severely impaired especially when considering that the respiratory muscles may consume as much as 40% of cardiac output in a patient with underlying cardiac disease.

Principles and Goals of Mechanical Ventilation

The history of mechanical ventilation was first cited by Galen, and he was the first person to describe mechanical ventilation (Cheifetz 2003). However, there is also evidence that demonstrates Avicenna, a Persian physician, described tracheostomy, oropharyngeal intubation, and upper airway secretion clearing, all to treat stridor and respiratory distress (Aziz et al. 2000; Golzari et al. 2013; Dabbagh et al. 2014).

The main objective for implementing mechanical ventilation is to use life support devices or

respiratory assist maneuvers (or technologies) for supporting ventilation (partially or totally) in such a way that the physiologic compromise in respiratory function of the patient could be compensated for and/or improvements in patient comfort occurs (Villar et al. 2007; Pediatric Acute Lung Injury Consensus Conference Group 2015).

During the postoperative period after pediatric cardiac surgery, the recovery period after post-cardiopulmonary bypass along with the gradual diminution of inflammatory response and edema is the primary rationale for ventilatory support. Mechanical ventilation may entail positive pressure ventilation or any other supportive respiratory maneuvers used for the assistance of ventilation.

In general, the main indications for utilization of mechanical ventilation include the following:

- ***Respiratory-related:*** these include apnea, bradypnea, hypoventilation, chronic pulmonary lung disease, impaired oxygen, and CO_2 exchange leading to respiratory failure, respiratory exhaustion, and impending arrest.
- ***Cardiopulmonary support*** and ***cardiac indications*** for installing mechanical ventilation: cardiopulmonary arrest, low cardiac output syndrome mandating the removal of the work of breathing due to impaired ventricular function.
- ***Neurologic*** indications when the central nervous system drive of ventilation is impaired or when the level of consciousness is not appropriate enough leading to impaired protective reflexes and subsequent aspiration of the secretions and impaired pulmonary toilet.
- ***Multi-organ disease*** impacting respiratory function/failure.
- ***Procedural-induced*** processes like post-cardiopulmonary bypass.

Based on the above indications, the main goals of mechanical ventilation could be summarized as follows:

- Optimizing **gas exchange** through optimization of pulmonary mechanisms, removing underlying shunts or V/Q mismatches, optimizing airway protection, and implementing the pulmonary toilet.
- Provide **cardiopulmonary support** during post-cardiopulmonary bypass transition, especially in low cardiac output, hemodynamically unstable patients, patients with inflammatory response, and patients with lung edema.
- Improve **patient comfort** (which includes decreasing respiratory distress, alleviating the degree of upper and/or lower airway obstruction, decreasing the amount of oxygen consumption, and alleviating respiratory fatigue).
- Decrease **work of breathing.**
- Preventing any possible **ventilator-induced injury** to the respiratory system (mainly the lungs).
- Administration of **inhaled pharmaceuticals or respiratory therapy.**

Ventilation Considerations and Unique Challenges in Congenital Heart Disease Patients

In congenital heart patients, several factors may coexist and complicate usual lung mechanics during artificial ventilation. These patients may have one or more issues affecting ventilation:

Mixed Lesions and Cardiac Shunts

Patients with shunts and mixed lesions may have simultaneous hypoxemia (i.e., right-to-left shunts) or pulmonary volume overload and overcirculation (i.e., left-to-right shunts). Cyanotic patients require additional maneuvers to prevent any increase in pulmonary vascular resistance; otherwise, the frequency and degree of cyanosis will be amplified. Additionally, measures must be taken in these patients to minimize pain, maintain normocarbia, and treat acidosis. The balance between pulmonary vascular resistance and systemic vascular resistance should be managed to prevent right-to-left shunting.

On the other hand, some patients have *shunt-dependent pulmonary or systemic circulation;*

therefore, sophisticated care should be taken to prevent shunt closure. Shunt closure may negatively impact hemodynamic stability and acidosis may develop. Organ ischemia may occur due to impaired perfusion distal to the shunt after its unplanned closure (e.g., patients with patent ductus arteriosus).

Another major challenge in these patients is the process of weaning and extubation in patients with mixing lesions and shunts. Infants who have shunt-dependent pulmonary blood flow and univentricular physiology are prone to a high rate of extubation failure (EF), and mainly due to cardiac and respiratory results of positive pressure ventilation they are much more determining (Gupta et al. 2014; Radke et al. 2020).

Perioperative Care of Single Ventricle Physiology (Hypoplastic Left Heart Syndrome (HLHS) and Fontan Procedure)

In recent years, the introduction of "fast-track" anesthesia for congenital heart diseases (CHDs) is being applied in the perioperative care of single ventricle patients. The clinical paradigm aims to allow early extubation or even "on the table" extubation with the use of multimodal analgesia techniques, coupled with spontaneous ventilation (i.e., negative pressure ventilation) to improve venous drainage after the operation, leading to improved postoperative hemodynamics, decreased length-of-stay, and earlier intensive care unit (ICU) discharge. On the other hand, if underlying pulmonary hypertension persists and inhaled nitric oxide (iNO) is going to be utilized, mechanical ventilation through the endotracheal tube (ETT) is the most favorable option. While iNO administration through nasal cannula or facemask is available, these methods are not the preferred route for iNO administration. Studies have shown that preoperative pulmonary hypertension is a risk factor for Fontan patients which may hinder earlier extubation; however, patients with univentricular physiology are prone to a high rate of extubation failure (Lofland 2001; Fiorito and Checchia 2002; Morales et al. 2008; Gupta et al. 2014).

Right or Left Ventricular Failure

Usually, congenital heart surgeries are definitive corrective procedures, and if managed properly, there is little chance for right or left ventricular failure. However, there are a considerable number of patients who are at risk for right or left heart failure; these patients may include those who have been clinically neglected, experienced treatment delays, sustained volume overload due to mixing lesions, or pressure overload due to obstructive lesions. Therefore, by the time these patients undergo surgery, the sequelae of volume and/or pressure overload are presented as right or left ventricular failure or even in worst cases, pulmonary hypertension. These patients may require assertive therapies including multimodal cardiac pharmacologic therapy, mechanical ventilation, ventricular assist devices, or even possible, heart or heart and lung transplant. The impact of ventricular failure, especially the left ventricle, on the lungs is a real challenge. Advanced discussion on assist devices and transplantation is discussed in chapter "Pulmonary Hypertension in Congenital Heart Diseases" (Pediatric Acute Lung Injury Consensus Conference Group 2015; Dalton and Macrae 2015; Emeriaud and Newth 2015; Essouri and Carroll 2015; Flori et al. 2015; Khemani et al. 2015; Quasney et al. 2015; Rimensberger and Cheifetz 2015; Sapru et al. 2015; Tamburro and Kneyber 2015; Valentine et al. 2015).

Fluid Management

Fluid therapy is among one of the most important issues in postoperative management especially given the effects of cardiopulmonary bypass and also, varying degrees of underlying cardiac abnormalities. Typically, fluid overload occurs early after cardiac surgical procedures and can lead to fewer ventilator-free days (VFDs), impaired oxygenation, impaired ventilation, lung edema, increased ICU stay, and impaired clinical condition. Additionally, worse outcomes are known to occur; therefore, prevention of *early* fluid overload can alleviate the occurrence of poor clinical outcomes (Arikan et al. 2012;

Hassinger et al. 2014; Seguin et al. 2014; Khemani et al. 2015; Sinitsky et al. 2015; Ingelse et al. 2016).

Strategies for Ventilation and Ventilator Modes

Whatever the indication for using mechanical ventilation, the following main issues should always be considered (Villar et al. 2007; Newth et al. 2009; Bagheri et al. 2016; van Kaam et al. 2021):

- Mechanical ventilation **does not have a therapeutic role**—instead, it is a *supportive* measure,
- The **process of weaning and extubation** should start at the first feasible and possible opportunity whenever the pediatric patient can sustain his/her spontaneous breathing.
- Mechanical ventilation always leads to **different degrees of lung lesions**. The endotracheal tube or other devices may require sedation, and prolonged intubation is associated with a considerable risk of infections and ventilator-associated pneumonia (VAP).
- **Cardiac-pulmonary sequelae** may occur, and the degree of the cardio-pulmonary lesion can range from mild-to-severe depending on the duration of ventilation and the technologies used for it.

Weaning, Readiness for Extubation, and Extubation Failure

Weaning Ventilator Support and Spontaneous Breathing Trials (SBT)

The weaning process should be managed using the following maneuvers or ventilation criteria, in combination with some monitoring methods including respiratory and hemodynamic monitoring:

- Rate of mechanical ventilation,
- Tidal volume (volume support ventilation weaning in volume-controlled modes),
- Pressure support (pressure support ventilation weaning in pressure-controlled modes),
- SBTs and continuous positive airway pressure (CPAP) (i.e., infants intubated for more than 3 days may require nasal CPAP, then nasal prongs after extubation).
- Extubation readiness test (ERT),

Keeping these issues in mind, current general practice favors maintaining moderate amounts of ventilator support during weaning in such a way that the patient may have some respiratory muscles rest and perform daily ERT (Feldman 2015; Kneyber et al. 2017; van Kaam et al. 2021).

However, the current practice of pediatric mechanical ventilation and weaning is often associated with a lack of explicit ventilator protocols. This practice is a "selective adoption of adult mechanical ventilation principles"; however, many aspects of these adult protocols are associated with major challenges or dilemmas when embraced in pediatric critical care. A recently published Cochrane systematic review by Wielenga et al. demonstrates that no evidence is available in supporting or rejecting "protocolled" over "non-protocolled" weaning on the duration of mechanical ventilation with invasive ventilation modes in newborn infants (Schindler 2005; Khemani and Newth 2010; Bennett et al. 2014; Khemani et al. 2015; Wielenga et al. 2016; Kneyber et al. 2017).

Prediction Tests for Extubation Success

The clinical tests used for the prediction of extubation were first used in research; however, they are currently used in clinical practice. There are currently three tests commonly utilized for the prediction of extubation success:

- **Rapid Shallow Breathing Index** (RSBI = f/Vt). This index was first described by Yang

and Tobin, and it has high sensitivity and low specificity which makes it a reliable screening test for successful weaning. The RSBI is a good practical predictor for extubation; higher RSBIs are predictive of extubation failure (Yang and Tobin 1991; Tobin and Jubran 2006; Newth et al. 2009).

- **Compliance, Resistance, Oxygenation, and Pressure (CROP) Index.** This index is another predictive measure for the assessment of the adequacy of ventilation. CROP index is calculated with 4 variables:

$$\text{CROP} = \text{Dynamic Compliance} \times \text{Maximal Negative Inspiratory Pressure} \times \left(\text{PaO}_2 / \text{PAO}_2\right) / \text{Respiratory Rate}$$

Lower CROP index values are predictive of extubation failure—especially with a CROP value of >/= 0.15 mL/kg/breaths/min (Baumeister et al. 1997; Thiagarajan et al. 1999; Newth et al. 2009; Emeriaud and Newth 2015).

- **Volumetric Capnography.** This technique employs the schematic of capnography that denotes the concentration of CO_2 in airway gas versus the volume of expiration. The slope of the diagram is used to calculate physiologic dead space (i.e., ratio of "Dead space/Tidal Volume" or "V_D/V_T"). If the V_D/V_T ratio is less than 0.05, extubation could be predicted successful; however, if the V_D/V_T ratio is more than 0.65, then extubation is predicted to be failed.

"Ready for Departure": Preparing for Extubation

Extubation criteria include some general clinical conditions and some measurable tests. Clinical criteria for extubation are noted in Table 1.

Common tests used for the assessment of extubation readiness include:

- Respiratory muscle strength demonstrated by negative inspiratory force (NIF),
- ETT "leak test" assesses the leakage of air around the endotracheal tube and checks for upper airway patency. Wratney et al. demonstrated that an air leak pressure >/=30 cm H_2O in the non-paralyzed patient (either in the time before extubation or during the time of mechanical ventilation) cannot predict an increased risk for extubation failure (Wratney et al. 2008; Kneyber et al. 2017).

Table 1 Clinical criteria for extubation

CNS and muscular system	• Wakefulness: the patient should be sufficiently awake • The tone of muscles should be working completely in such a way to grasp firmly the objects like the fingers of the examiner or produce a strong and forceful cough
Airway	• Patent upper airway is mandatory which is tested by performing an air leak test around the endotracheal tube • Airway reflexes intact in such a way that could protect the lungs from aspiration
Cardiovascular system	• Stable cardiovascular and hemodynamic parameters • The minimal dose of inotropes
Respiratory system	• Minimal respiratory secretions • The normal range for breath sounds • Ability to produce a strong and forceful cough • $SpO_2 > 94$ with minimal supplemental O_2 requirement (i.e., <30%) • Minimal need for pressure support (5–10 more than PEEP)
Water and electrolytes	• No significant blood gas and/or electrolyte abnormalities • Controlled water and loading status

The "Extubation Procedure"

The following maneuvers are basic steps in the extubation procedure:

- Ensuring the adequacy of clinical criteria for extubation (Table 1),
- Humidification regardless of the technique is strongly recommended before extubation in mechanically ventilated children (Kneyber et al. 2017),
- Positioning with 30–45° elevation of the head of the bed is strongly recommended unless there is any contraindication (Kneyber et al. 2017),
- Suctioning the airway before extubation is recommended; however, there is no specific "routine mode" or any recommended "superior approach" (Kneyber et al. 2017),
- Whatever suctioning approach is used, the risk of derecruitment during suctioning should be minimized (Kneyber et al. 2017),
- Suctioning of the oropharynx, nostrils, and endotracheal tube,
- Neither routine chest physiotherapy nor cough-assist techniques are necessarily considered standards of care just before extubation,
- Emptying gastric contents through suctioning of naso/oro-gastric tube,
- having nasal prongs on oxygen been fore extubation and preparing an oxygen facemask, to decrease the chance of immediate hypoxia,
- Ensuring available equipment for assisting ventilation devices (i.e., mask and bag attached to oxygen; devices for NIPPV or CPAP),
- Check for laryngoscope and different blades and blade sizes, different size tubes, and other ventilation devices to be available,
- Ensuring sedatives and muscle relaxants are available,
- Nebulizers, including epinephrine and other agents, to be available,
- Selected corticosteroids should be available as bolus and infusion doses to decrease any hoarseness or respiratory distress,
- Diuretics should be available to treat volume overload and respiratory distress; corticosteroids may prevent or treat post-extubation stridor in neonates or children (Khemani et al. 2009),
- Respiratory monitoring including arterial blood gases should be available,
- Describe the procedure for parents.

Predictors of Extubation Failure

Extubation failure (EF) is defined as "**reintubation within 24–72 h.**" Based on pediatric studies, a failed extubation rate of less than 10% is accepted as the norm (Kurachek et al. 2003; Rothaar and Epstein 2003; Newth et al. 2009; Artime and Hagberg 2014; Saikia et al. 2015). However, the rate of EF could be significantly higher in the "extremely preterm infants" (Kidman et al. 2021b). Regardless of the rate of EF, the trend of pediatric EF has significant differences compared to adults, including:

- Majority of pediatric patients weaned from mechanical ventilation in 2 days or less,
- RSBI, CROP, and Volumetric Capnography, though considered criteria for prediction of extubation success, could be used as measures of prediction for EF.
- Protocols used in adult weaning with a significant effect on extubation trend ***do not have a significant effect*** on the time for weaning in pediatrics and neonates. There is a paucity of evidence in supporting or rejecting the effects of "protocolled" over "non-protocolled" weaning regarding the duration of mechanical ventilation in children,
- EF rate does not have a significant difference between pressure support ventilation weaning, volume support ventilation weaning, or other methods.
- Obstruction of the upper airway is claimed as the most common etiologic factor for EF (Newth et al. 2009),
- The incidence of EF is higher in these patients:
  - **Neonates and infants**; especially those with underlying morbidities, lower gestational age, or prematurity; also, Kidman et al. demonstrated that a "lower Gestational

Age (GA) and a higher pre-extubation measured Mean Airway Pressure (MAP)" could be a good prediction index for EF in extremely preterm infants (Kidman et al. 2021a),
- Patients with underlying **cyanotic congenital heart disease,**
- Patients under **prolonged** mechanical ventilation,
- Patients with **increased RSBI**, inadequate cough **reflex**, and thick unmanageable **secretions** have an increased risk for EF and could be used as predictive measures (Thiagarajan et al. 1999; Randolph et al. 2002; Rothaar and Epstein 2003; Newth et al. 2009; Khemani and Newth 2010; Artime and Hagberg 2014; Gupta et al. 2014; Saikia et al. 2015; Wielenga et al. 2016).

Noninvasive Ventilation

Nasal Cannula

Nasal cannulas, nasal prongs, or RAM™ cannulas can deliver supplementary oxygen to the patent in relatively low amounts. They are mainly oxygen administration is necessary but the desired FiO_2 is low. FiO_2 increase by nasal prongs depends mainly on oxygen flow and the pattern of respiration of the patient (Table 2).

Table 2 Estimates of fraction of inspired oxygen (FiO_2) with nasal prongs

Oxygen flow (Liters per minute)	Highest achievable FiO_2
1	24%
2	27%
3	30%
4 (*needs humidification*)	33%
5 (*needs humidification*)	35%
6 (*needs humidification*)	38%

RAM™ cannula can mimic CPAP when the nostrils are partially occluded by the cannula. Some studies favor this technique while others do not (Iyer and Chatburn 2015; Nzegwu et al. 2015; Aktas et al. 2016; Gerdes et al. 2016)

Neonatal Continuous Positive Airway Pressure (nCPAP)

nCPAP is a special CPAP used for neonates when aiming for use of a noninvasive ventilation mode with the following goals:

- Improving oxygenation status,
- Increasing functional residual capacity (FRC),
- Decreasing intrapulmonary shunts,
- Decreasing the degree of alveolar collapse,
- Decreasing ventilator-induced lung injury (VILI),
- Decreasing the incidence of lung complications like VAP,
- Decreasing the chance for reintubation,
- Reducing the rate of readmission to the critical care unit,
- Decreasing mortality.

More than 40 years have passed since the invention of nCPAP; however, during the last few years, significant improvements have been made. The two most influential factors affecting outcomes in neonates treated with nCPAP are the "clinicians' abilities to perceive changes" which occur in the pathophysiology of the infants who are under treatment with nCPAP and "quality of airway management." Some studies have demonstrated that careful patient selection is associated with the level of training and experience in the ICU team and that may affect the outcome. Some studies suggest that nCPAP and other noninvasive methods are effective in preventing reintubation in neonates and infants after cardiac surgery. However, there is a significant difference between alternative modes of nCPAP and other noninvasive modes of ventilation. Additionally, the risk of nasal injury and sternal dehiscence in neonates are documented. (Kurt et al. 2008; Diblasi 2009; Squires and Hyndman 2009; Zarbock et al. 2009; Boeken et al. 2010; Pelosi and Jaber 2010; Drevhammar et al. 2012; Bancalari and Claure 2013; Kidman et al. 2021b).

A Cochrane systematic review published in 2014 has compared noninvasive positive pressure

ventilation (NIPPV) with nCPAP for preterm neonates after extubation (Lemyre et al. 2014). The meta-analysis demonstrated the following findings:

- Clinical signs of extubation failure are significantly less common after using NIPPV compared with nCPAP,
- Reintubation within 2–7 days after extubation is less with NIPPV,
- these differences do not affect chronic lung disease or mortality rate,
- Synchronization therapy may have an important role in NIPPV.

High Flow Nasal Cannula (HFNC)

HFNC has been extensively used in pediatric ICUs during the last 10 years, and it has more gradually been replacing nCPAP due to its simple basics of function and excellent tolerance by the patients. HFNC delivers humidified and warm air which is much better tolerated than cold air. HFNC delivers a high flow rate of heated (34 °C and 37 °C) and humidified gas, often as much as 2 L/kg/min of blended air and oxygen which is heated and humidified. Studies have shown that it can improve the respiratory function in the following ways: (Manley et al. 2013; Yoder et al. 2013; Milesi et al. 2014; Wilkinson et al. 2016; Hehsan et al. 2022):

- Washout of dead space in the nasopharynx,
- Improved gas exchange,
- Clearance of the pulmonary mucociliary tract,
- Lung oxygen delivery,
- Humidification of delivered gases to the lungs,
- Improved breathing pattern and decreased work of ventilation and breathing,
- Post-extubation ventilatory support.

There are some controversies about the efficacy of HFNCs. For example, two different Cochrane Database Reviews published in 2014 have somewhat questioned (with different degrees of uncertainty) the efficacy of HFNC for infants and children with bronchiolitis. (Beggs et al. 2014; Mayfield et al. 2014). On the other hand, a Cochrane Database Review published in 2016 concluded that using HFNC could be useful as post-extubation support, with a decreased chance of nasal trauma and pneumothorax in comparison with nasal CPAP (Wilkinson et al. 2016).

Miscellaneous Issues

Extra-Corporeal CO_2 Removal (ECCO2R)

ECCO2R is a partial respiratory support technique that can help remove carbon dioxide out of the blood using low levels of blood flow through an extracorporeal circuit with minimal effects on blood oxygenation (Boyle et al. 2018). In patients under mechanical ventilation, there is always the chance for ventilator-induced lung injury (VILI). There are some ventilation modalities to counteract VILI. Among them, ultra-protective ventilation strategies could be employed which result in normal peak inspiratory pressure, very low tidal volumes, near-normal lung oxygenation, and lower values for minute ventilation; this leads to nearly appropriate oxygenation, although hypercarbia may remain a problem. ECCO2R is often used as part of ultra-protective ventilation strategies to remove CO_2 from the body and compensate for CO_2 accumulation in ultra-protective ventilation strategies. In ECCO2R, the amount of blood being perfused is very much lower than the amount of perfusion provided by extracorporeal membrane oxygenation. Although ECCO2R is not a new modality, during the last years, its application in association with ultra-protective ventilation strategies has gained more popularity (Habashi et al. 1995a, b; Kaushik et al. 2012; Camporota and Barrett 2016; Deniau et al. 2016; Taccone et al. 2017).

High-Frequency Ventilation or High-Frequency Oscillatory Ventilation (HFV or HFOV)

HFV or HVOF offers a protective measure in the perioperative care of pediatric patients with congenital heart disease children who have sustained lung injury. HFV or HFOV uses very small tidal volumes and a high rate of ventilation to keep airway pressure at the most modest possible level. Though the institution of HFV is delayed, there is a shift towards early use of HFV during the last years. However, there is still a paucity of evidence to demonstrate improved outcomes in the early institution of HFV concerning lung protection (Fessler et al. 2008; Khemani and Newth 2010).

Based on the systematic review and meta-analysis, the available evidence scarcely supports that HFV can decrease mortality and length of stay in critically ill children beyond the newborn period (Duyndam et al. 2011). Another Cochrane database systematic review also showed that no controlled trial supports the use of HFOV in term or near-term infants with severe pulmonary dysfunction (Henderson-Smart et al. 2009).

Inhalational Routes of Drug Delivery

The number of drugs that can be administered through the inhalational route is an ever-increasing list. The application of newly designed targeted therapies, including nanostructured materials and nanostructured carriers, has only broadened therapeutic options. (Dabbagh and Rajaei 2011). The following are drugs currently being used as inhalational therapies:

- iNO and treprostinil are used for the treatment of pulmonary hypertension,
- Inhaled insulin (White et al. 2020),
- Exogenous surfactant either through the endotracheal tube or using a nebulizer has been proposed with varying degrees of effect (Rong et al. 2020),
- Antibiotics including inhalational ciprofloxacin encapsulated in liposomes and anti-tuberculosis drugs cause a "massive reduction" of drug dose and decreased toxicity (Wood 1991; O'Callaghan 1994; Rastogi et al. 2006; Gupta and Ahsan 2010; Dabbagh and Rajaei 2011; Petkar et al. 2011; Stream and Bull 2012; Hamblin et al. 2014; Brashier et al. 2015).

Chest Physiotherapy

In patients undergoing congenital cardiac surgeries, using standard protocols for physiotherapy might improve pulmonary status; physiotherapy. Even aerobic exercise can be useful in improving exercise capacity and, also, postoperative pulmonary function, and cardiopulmonary fitness; however, it is still controversial. Several systematic reviews that there is no evidence that the use of prophylactic respiratory physiotherapy in the prevention of pulmonary complications after cardiac surgery is effective (Pasquina et al. 2003; Nagarajan et al. 2011; Kaminski et al. 2013; Duppen et al. 2015; Kneyber et al. 2017).

Chronic Respiratory Failure and Tracheostomy

The first introduction of tracheostomy dates back to its use by Medieval Islamic physicians (Golzari et al. 2013; Dabbagh et al. 2014). The recently published analysis of the "***Society of Thoracic Surgeons Congenital Heart Surgery Database***" demonstrated an increasing rate of tracheostomy associated with CHD and congenital heart surgery. The main indications for tracheostomy were divided as preoperative indications (i.e., prematurity, genetic anomalies, and preoperative mechanical ventilation) versus. postoperative indications (i.e., cardiac arrest, modes of extracorporeal support, injuries to the phrenic or laryngeal nerves, and neurologic insults). Based on this report, the operative mortality was 25% (Donnelly et al. 1996; Al-Samri et al. 2010; Mastropietro et al. 2016).

On the other hand, when speaking about different aspects of tracheostomy in congenital heart

surgery, the following items are still among the most controversial issues for tracheostomy, including pediatric surgery ICU wards:

- **Timing (early versus delayed):** the only justified indication for early tracheostomy is patient comfort (Donnelly et al. 1996; Kremer et al. 2002; Al-Samri et al. 2010).
- **Indications**: prolonged ventilation is the most common indication for pediatric tracheostomy, though it has many controversial issues due to its risk/benefit assessments. Other less common indications include using the need for aerosolized/inhalation treatments, nosocomial pneumonia, witnessed aspiration events needing emergent tracheostomy, and repeated reintubations (Donnelly et al. 1996; Kremer et al. 2002; Al-Samri et al. 2010).
- **Techniques:** unless there is a life-threatening emergency, pediatric tracheostomy is a procedure that should be done electively in the operating room while the patient is intubated (Donnelly et al. 1996; Kremer et al. 2002; Fraga et al. 2009).
- **Risks/benefits**: benefits of tracheostomy include patient comfort, mobility, speech, oral ingestion, improved suctioning of the airway, decreased airway resistance and more secure airway, improved weaning process from mechanical ventilation, and decreased rate of VAP. The main etiologies for tracheostomy-related death include cannula obstruction and accidental decannulation; however, the most frequent early complications are pneumomediastinum, pneumothorax, wound-related complications, and tracheostomy site bleedings. Common late complications include tracheal stenosis and the formation of granulation tissue (Donnelly et al. 1996; Kremer et al. 2002; Al-Samri et al. 2010; Mastropietro et al. 2016).

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Cardiac Anesthesia in Infants and Children: Postoperative Bleeding and Coagulation Management

Pablo Motta and Antonio Pérez Ferrer

Abstract

Postoperative bleeding is the most common complication after pediatric cardiac surgery. Up to 5% of cardiac surgery will require re-exploration for significant blood loss in the first 24 h after surgery. If not addressed early, uncontrolled bleeding could lead to hypovolemic shock, multi-organ failure, and eventually death. Concealed bleeding in the chest could also cause cardiac tamponade if the chest and mediastinum are not adequately drained. Blood product use is not devoid of complication, and strategies should be designed to minimize transfusion as much as possible. There are several known medical and surgical risk factors for postoperative bleeding. The anesthesiologist should investigate "red flags" for postoperative bleeding during the preoperative visit and address them. Unnecessary medications that could affect coagulation should be discontinued. Medical conditions that affect the coagulation system should be stabilized. Cardiopulmonary bypass (CPB) strategies and surgical plans should also consider the effect on bleeding and coagulation. Finally, it is essential to plan for adequate intravenous access, use of prophylactic agents and secure blood availability, coagulation factors, and components.

Keywords

International normalized ratio · Postoperative bleeding · Fresh freeze plasma · Prothrombin complex concentrate · Ventricular assist device

Introduction

Clinical monitoring for intraoperative bleeding starts as soon as heparin is reversed by surgical inspection of the operative site. Once the chest is closed, monitoring the chest tube output (CTO) is of paramount importance. An acceptable CTO is less than 1–2 mL/kg/h even, though it could be higher in the first 2 h (3–4 mL/kg/h). Bercovitz et al. defined excessive postoperative bleeding in infants undergoing cardiac surgery with cardiopulmonary bypass (CPB) as CTO > 7 mL/kg/h for ≥2 consecutive hours in the first 12 postoperative hours and/or > 84 mL/kg total for the first 24 postoperative hours and/or surgical re-exploration for bleeding or cardiac tamponade physiology in the first 24 postoperative hours (Bercovitz et al. 2018).

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Therefore, bleeding should be prevented and addressed early to avoid blood products administration. Increasing literature shows that allogeneic blood transfusions are associated with thrombosis, acute renal failure (ARF), transfusion-related immunomodulation (TRIM), transfusion-related acute lung injury (TRALI), and transfusion-associated circulatory overload (TACO). Consequently, perioperative blood transfusion is associated with worse outcomes. In addition to reoperation, bleeding complications in cardiac surgery are associated with postoperative stroke, mechanical ventilation, intensive care unit (ICU) stay, 30-day ICU mortality, and hospital cost (Christensen et al. 2012, Christensen et al. 2009; Faraoni et al. 2019a; Guay and Rivard 1996; Guzzetta et al. 2008; Hayashi et al. 2011; Thiele and Raphael 2014).

Risk Factors for Postoperative Bleeding

Several preoperative risk factors for postoperative bleeding pediatric cardiac surgery can be classified as specific to the patient, congenital heart disease (CHD), and those related to the surgical procedure and cardiopulmonary bypass (CPB) (Table 1).

Preoperative Risk Factors

Age is inversely related to the risk of bleeding. Neonates and particularly premature babies are the highest-risk groups for postoperative bleeding. Neonates do not have a wholly developed coagulation system at birth. There is a balance

Table 1 Risk factors for postoperative bleeding

Preoperative factors		
Age	Neonates Premature Low birth weight	Undeveloped coagulation system and calcium hemostasis
Comorbidities	Acquired coagulopathies	Dilution and trauma post CPB Renal or hepatic insufficiency
	Congenital coagulopathies	von Willebrand disease
Medications	Antiplatelets agents	Aspirin < ADP-receptor antagonist < GPIIb/GPIIIa inhibitor
	Anticoagulants	LMWH Direct factor X inhibitors Thrombin inhibitors vitamin-K antagonist
Intraoperative factors		
Procedure-related	Neonatal repairs	Norwood, ASO Truncus repair TAPVR
	Single-ventricle palliation	Glenn shunt Fontan
	Aortic reconstruction	Multiple suture lines
	Redo surgery	Numerous adhesions
	ECMO/VAD	
CPB related	Hemodilution	Major effect in infants
	Hypothermia	DHCA
	Coagulation derangements	Hyperfibrinolysis Residual heparin Protamine overdose

CPB cardiopulmonary bypass, *LMWH* low molecular weight heparin, *ASO* arterial switch operation, *TAPVR* total anomalous pulmonary venous return, *ECMO* extracorporeal oxygenation, *VAD* ventricular assist device, *DHCA* deep hypothermic circulatory arrest

between the low endogenous procoagulants and anticoagulant systems (Arnold 2014). In addition, neonates do not regulate calcium hemostasis well, essential in the coagulation process (Jain et al. 2010). Traditional coagulation testing such as prothrombin time (PT), thrombin time (TT), and activated partial thromboplastin time (aPTT) are prolonged in neonates (Long et al. 2011). Refer to chapter "Khorgamielectrocardiography: Basic Knowledge with Focus on Fetal and Pediatric ECG" for extensive discussion regarding preoperative testing.

Congenital coagulopathies (e.g., von Willebrand disease) or acquired coagulopathies secondary to diabetes and liver or kidney dysfunction increase the bleeding risk.

Single-ventricle patients in the pre-Fontan stage have coagulation anomalies characterized by lower protein C, protein S, antithrombin III, and factors II, V, VII, and X and longer prothrombin times probably due to chronic passive congestion of the liver. These factor anomalies correct post-Fontan surgery, probably due to improved systemic oxygenation and overall perfusion (Cheung et al. 2005). Cyanotic heart disease is associated with secondary erythrocytosis as a compensatory mechanism for hypoxemia (Zabala and Guzzetta 2015). This compensatory increase in the red cell mass reduces the plasma volume with the consecutive reduction in coagulating factors, fibrinogen, and platelet count, increasing the postoperative bleeding risk. The effect on coagulation is directly related to the amount of hypoxia and polycythemia. Cyanotic patients with multiple aortopulmonary collateral vessels have an increased venous return to the heart. This venous return affects surgical visualization and increases postoperative bleeding due to poor surgical hemostasis (Dönmez and Yurdakök 2014).

Pediatric patients with congenital heart disease are commonly on antiplatelet agents or anticoagulants, implicated in increasing bleeding. Of the antiplatelets, aspirin has a lower risk of bleeding, the adenosine-diphosphate (ADP)-receptor antagonist has an intermediate chance, and the GPIIb/GPIIIa receptor antagonists have the highest risk. Aspirin causes irreversible inhibition of the platelet cyclooxygenase 1 (COX1), which is responsible for the formation of thromboxane A_2, essential for platelet activation and aggregation. Aspirin duration of action is related to the platelet turnover (about 10 days) because the inhibition is not reversible. About 10% of the platelet COX1 activity recovers per day due to platelet turnover, and only 20% of the platelet COX1 activity is needed to achieve normal hemostasis (Awtry and Loscalzo 2000). ADP-receptor antagonist such as clopidogrel affects the geometry of the platelets, making them spherical and unable to aggregate. Therefore, GPIIb/GPIIIa receptor antagonists are used infrequently in pediatrics (Wijeyeratne and Heptinstall 2011). Still, they will also increase the risk of bleeding due to the profound capacity to prevent platelet aggregation, thrombus formation, and distal thromboembolism. Alternatively, early withdrawal of aspirin or clopidogrel is not feasible in shunt-dependent patients at life-threatening risk for thrombosis.

Similarly, in emergency cases like a heart transplant with harvesting of left ventricular assist device (VAD), the patient undergoes surgery under full anti-aggregation and anticoagulation. Preoperatively the platelet count in these patients is expected to be normal since the production is not affected. Platelet functional studies such as PFA-100 and multiple platelet aggregometer, which are described at length in chapter Khorgamielectrocardiography: Basic knowledge with focus on fetal and pediatric ECG, can detect platelet inhibition but are not used routinely in the preoperative period. Platelet aggregation studies showed conflicting data in terms of predicting not postoperative blood loss and more research is needed (Hofer et al. 2011; Orlov et al. 2014). Recently, in adults undergoing heart surgery, low platelet activity predicted 30-day mortality, bringing up the question to when to discontinue the antiplatelet agents (Kuliczkowski et al. 2016).

Anticoagulants and antiplatelet are medications strongly associated with postoperative bleeding. Unfractionated heparin (UH), a mixture of polymers of sulfated glycosaminoglycans (molecular weight 5–30 kDa), potentiates the anticoagulant effects of antithrombin III. Unfortunately, heparin has a short half-life

since it is cleared from circulation by endothelial cells by a saturable mechanism and by kidney excretion. Due to the extensive metabolism, UH is administered as a bolus and followed by an infusion. Target aPTT is 1.5–2 baseline values. Heparin is usually stopped 6 h before surgery, and residual effects can be checked by the activated clotting time (ACT) in the operating room. Typical ACT values are 80–160 s. Heparin concentration measurement in pediatrics has not correlated well with anti-factor Xa activity and is not commonly used to detect a residual UH effect (Gruenwald et al. 2000).

Low molecular weight heparin (LMWH) is a depolymerized molecule with an average weight of 5 kDa, in which the inhibition of factor Xa mediates its effect. Due to the lack of monitoring needed, longer half-life, and predictable results, LMWH has gained popularity in the pediatric population. LMWH should be held 12 h before surgery, and if required, its residual effect can be checked by the anti-factor Xa levels (0.5–1.0 U/mL therapeutic, 0.1–0.3 U/mL prophylactic).

Direct factor X inhibitors have limited indications in pediatrics, and their use has been restricted to heparin-induced thrombocytopenia. Due to its long half-life and lack of an antidote, these drugs are not ideal to be used in the preoperative period (Young 2008).

Vitamin-K antagonists like coumadin inhibit the production of vitamin-K-dependent coagulation factors (II, VII, IX, and X). In addition, Coumadin also inhibits the production of physiologic anticoagulant proteins C and S. Its effect is monitored by the international normalized ratio (INR). Therapeutic INR values depend on the indication (INR 2–3 thromboembolism, INR 2.5–3.5 mechanical valve). Vitamin-K antagonist's long half-life makes it impractical for the perioperative period and is usually held for 3–5 days and transitioned to UH. Suppose emergency cardiac surgery is needed in a patient on coumadin. In that case, its effect can be reversed with prothrombin complex concentrate (PCC), which will be discussed later in the chapter.

Intraoperative Risk Factors

The intraoperative risk factors for bleeding are related to the procedure and the cardiopulmonary bypass. Complex surgeries by RACHS-1 score such as neonatal repairs (e.g., Norwood, arterial switch, truncus repair, and total anomalous pulmonary vein repair), single-ventricle palliation (Glenn Shunt and Fontan), redo surgeries, and aortic surgeries are the highest risk for perioperative bleeding (Guay and Rivard 1996; Guzzetta et al. 2015). In addition, the duration of surgery has been related to postoperative bleeding measured by CTO and rotational thromboelastometry (ROTEM) trace abnormalities (Hayashi et al. 2011).

The ultimately high postoperative bleeding patients are those on mechanical circulation either extracorporeal membrane oxygenator (ECMO) or VAD. ECMO patients are kept fully anticoagulated on UH infusion to avoid thrombosis triggered by the exposure blood components with the ECMO circuit. In addition to coagulation activation, there is a dilutional effect on coagulation factors due to the ECMO prime. The target values for anticoagulation while on ECMO are ACT of 180–220 s, anti-factor Xa levels of 0.3–0.7 IU/mL, and aPTT of 1.5–2.5 times the normal. Most of the ECMO circuits are heparin coated decreasing the amount of UH needed. Low levels of anticoagulation could lead into ECMO circuit thrombosis, but on the other hand, excessive anticoagulation could lead to bleeding. Neurological injury due to central nervous system (CNS) bleeding is the most feared complication of ECMO and a frequent cause of withdrawing support.

There are shortcomings with the use of UH anticoagulation for ECMO in neonates and children's due to their lower serum levels of antithrombin triggering heparin resistance (Goswami et al. 2020). The alternative agents are direct thrombin inhibitors such as bivalirudin that produce a more reliable anticoagulation since it does not require a cofactor as antithrombin. Additionally, bivalirudin binds both circulating and clot-bound fibrin. The drawback of using bivalirudin is that there is no available reversal

agent but has a very reliable pharmacokinetics (elimination half-life 25 min in adults). Bivalirudin is mostly cleared by the kidney either unchanged or after undergoing intracellularly proteolysis (Robson et al. 2002). Bivalirudin is administered by continuous infusion at 0.3 mg/kg/h. Patient with renal dysfunction will decrease the dose in half. Bivalirudin anticoagulation effect is monitored by aPTT with a target of 58–78 s checked every 4 h. There is some limited evidence that anticoagulation with bivalirudin in pediatric patients on ECMO may be associated with less bleeding that UH (Hamzah et al. 2020).

VAD patients are at increases risk from bleeding, thrombosis, and emboli from the device, cannulas, and valves. Paracorporeal devices (e.g., Berlin Heart) due to their complexity have a particular risk for thrombosis and emboli. The traditional anticoagulation regiment for VAD patients was the Edmonton triple antithrombotic protocol entailing aspirin, dipyridamole, and either warfarin ≥12 months or enoxaparin <12 months. Rosenthal et al. compared the Edmonton with Stanford modified anti-thrombotic guideline which included triple anti-platelet therapy (adding clopidogrel) and low-dose steroids for inflammation if needed (Rosenthal et al. 2017). The cohort using the Stanford modified anti-thrombotic guideline had a decreased incidence of stroke without increasing the bleeding rate. Recently, Vanderpluym et al. showed that the used of direct thrombin inhibitors might decrease the risk of thrombosis and emboli without a major rise in bleeding (VanderPluym et al. 2020).

During VAD harvesting for heart transplantation coagulation point-of-care (POC), testing is crucial to minimize the bleeding risk and conduct a coagulation goal-directed therapy (Annich and Adachi 2013; Esper et al. 2014; Seibel et al. 2008).

Cardiopulmonary bypass (CPB) causes massive physiologic changes in children characterized by hemodilution, coagulation activation, and hyperfibrinolysis (Sniecinski and Chandler 2011). The hemodilution effect is inversely proportional to size, neonates and infants being the ones affected the most (Table 2). The artificial surface of the CPB circuit activates platelets and the kallikrein-kinin system promoting thrombosis (Fig. 1). Heparin use even though effective to avoid circuit thrombosis and thrombin formation does not inhibit completely platelet and coagulation activation.

Bivalirudin has been used as an alternative to heparin in pediatric CPB in patients. The recommended bolus dose is the 1 mg/kg bolus followed by a 2.5 mg/kg/h infusion and 50 mg administered to the pump prime. Additional amounts to maintain target ACTs are commonly needed (Zaleski et al. 2019). There is no antidote to bivalirudin so the effect will wear off slowly with ACT normalization in 2 h. In a randomized controlled trial of heparin versus bivalirudin anticoagulation in acyanotic children undergoing open-heart surgery, Hasija et al. demonstrated that bivalirudin does not increase postoperative bleeding (Hasija et al. 2018).

During the CPB run, there is also platelet sequestration, downregulation of GPIIb/GPIIIa receptor, and destruction due to thrombogenic bypass circuit surfaces. Due to these facts, platelet function and fibrinogen concentration are affected the most post CPB in pediatric cardiac surgery (up to 50% of baseline values). An early

Table 2 Priming volume hemodilution effect by weight

Flow (mL/min)	Weight (kg)	CPB circuit	Priming volume (mL)	Hemodilution (%)
0–500	0–6	3/16″ art 1/4″ ven	~350 mL	70–137
500–1000	6–7	1/4″ art and ven	~450 mL	76–88
1000–2000	7–15	1/4″ art 3/8″ ven	~650 mL	54–111
2000–3000	15–18	1/4″ art 3/8″ ven	~850 mL	59–70
3000–4000	18–25	1/4″ or 3/8″ art, 3/8″ ven	~1200 mL	64–83

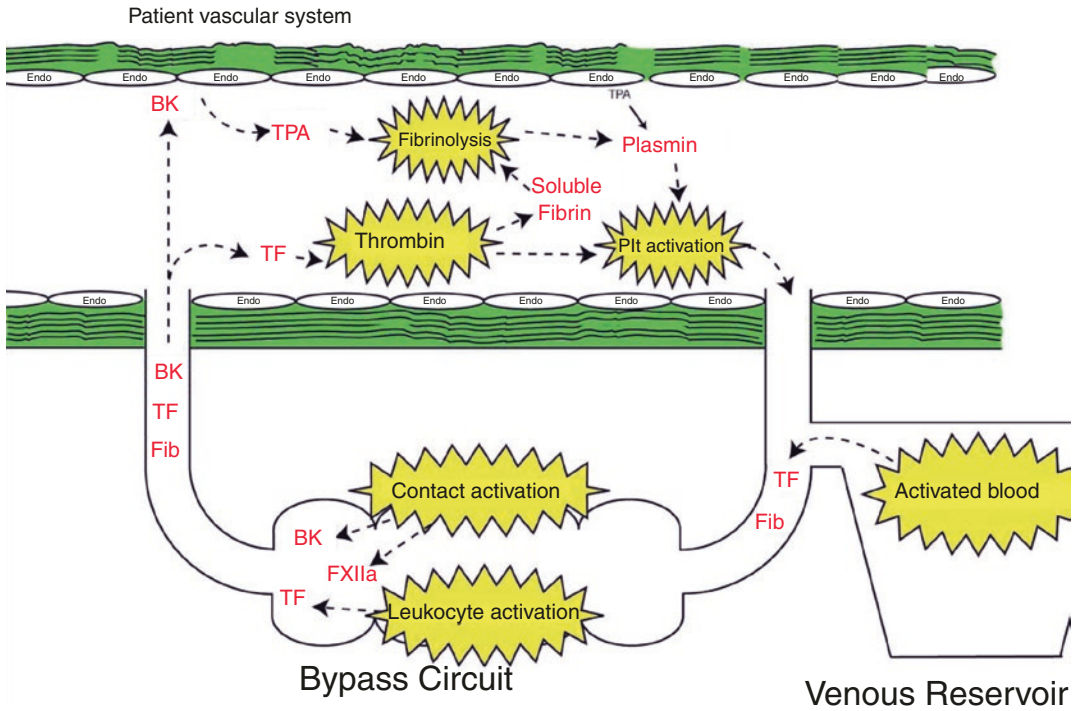

Fig. 1 Summary of hemostatic activation mechanisms on cardiopulmonary bypass (C.P.B.). *B.K.* bradykinin, *FXIIa* activated factor XII, *TF* tissue factor, *T.P.A.* tissue plasminogen activator, *Plt* platelets, *Fib* fibrin degradation products, *Endo* endothelium. (Details provided in text Published with permission from Wolters Kluwer Health, Inc. (Sniecinski and Chandler 2011))

study by Miller et al. showed that platelets and cryoprecipitate (rich in fibrinogen) restore hemostasis in the initial post CPB period (Miller et al. 1997, 2000). Infant CPB is conducted under some degree of hypothermia for most procedures and in some cases (e.g., aortic reconstruction—Norwood) under deep hypothermia circulatory arrest (DHCA). Mossad et al. showed that when comparing with adult cardiac surgery, pediatric patients have a higher incidence of DHCA use and blood transfusion requirements in the perioperative period (Mossad et al. 2007). Coagulation and inflammation activation is caused by the stress caused by the trauma of the circulating blood components with the artificial surface of the CPB circuit. Due to immaturity of coagulation and immune system, this activation is more profound in neonates and infants. Modulation of the stress response with intravenous steroid is common practice even though there is doubtful evidence for its use. Steroid will decrease the inflammatory mediator's interleukin-1, interleukin-6, interleukin-8, tumor necrosis factor, leukotrienes, and endotoxin, but its effects on coagulation and postoperative bleeding are not well defined (Augoustides 2012). Gibson et al. in a recent database review on prophylactic corticosteroids in children (0–18 years) undergoing cardiac surgery with CPB showed no effect in mortality, length of postoperative ICU, and hospital stay (Gibbison et al. 2020).

The priming solution varies with patient size and weight. Regularly, prime solution for patients <18 kg includes packed red blood cells (PRBC), crystalloids (e.g., PlasmaLyte), colloid (e.g., albumin), and/or fresh frozen plasma (FFP), trying to keep the solution as physiological as possible. In addition to the prime solution

heparin, buffer solution (e.g., sodium bicarbonate), mannitol, and steroids are added. The use of FFP for CPB prime is debatable. Traditionally, FFP is added to blood prime in patients <18 kg, but there is no evidence that this practice will improve outcomes and decrease postoperative bleeding. Desborough et al. in a Cochrane database of systematic reviews showed that in patients without coagulopathy, the addition of FFP did not improve the outcome (Desborough et al. 2015). Miao et al. showed that adding FFP to the CPB in a population of cyanotic patient (6 months–3 years) undergoing cardiac surgery did not decrease postoperative bleeding. Preoperative fibrinogen was an independent predictor of postoperative blood loss (Miao et al. 2014). Lately, Dieu et al., in the first double-blinded study of pediatric patients undergoing cardiac surgery with CPB, showed that postoperative bleeding and the transfusion needs were similar independently of the type of CPB prime either crystalloid or FFP (Dieu et al. 2020).

Pathophysiology of Postoperative Bleeding

Cardiac surgery exposes the sub endothelium, which is rich in thromboplastin, triggering platelet activation and aggregation binding to the von Willebrand factor and collagen forming the initial vascular plug. The coagulation system through the factors IX (FIXa) and factor X (FXa) is activated by the binding of the wound tissue factor (TF) to active factor VII (FVIIa) transforming prothrombin to thrombin. The activated platelets, factors V, VIII, and XI, work as catalyst accelerating the coagulation process. Next the clot stabilizes with fibrinogen and factor XIII. Finally, once the clot is formed and stable, the fibrinolytic system avoids further thrombus formation (Fig. 2).

Uncontrolled surgical bleeding can lead to coagulation activation by exposure of the sub endothelium, coagulation factor loss, and thrombocytopenia. Blood product replacement should be balanced (e.g., packed red blood cells, coagulation factors, fibrinogen, and platelets) and POC targeted. Isolated PRBC replacement further dilutes coagulation factors, fibrinogen, and platelets perpetuating the vicious circle of coagulopathy and further bleeding. Hypothermia, acidosis, low-ionized calcium, and hyperfibrinolysis should also be tackled since they are major contributors of maintaining the postoperative bleeding cycle. CPB rewarming strategies are crucial since infants are prone to hypothermia due to widespread use of hypothermia and DHCA in pediatric cardiac surgery. Neonates and infants due to limited fat stores, inability to shiver, and larger ratio of body surface area to weight are especially susceptible to hypothermia. Hypothermia affects coagulation factors and platelet function perpetrating postoperative bleeding. Additionally, uncorrected hypothermia will increase oxygen consumption causing metabolic acidosis impairing hemostasis even further. Hypocalcemia is common in infants due to sarcoplasmic reticulum underdevelopment and reduced calcium storages. Furthermore, massive use of citrated blood product will decrease ionized calcium even further (Kozek-Langenecker 2014). Residual heparin effect due to reheparinization and/or excess protamine has also been associated to postoperative bleeding. Lastly hyperfibrinolysis in pediatric cardiac surgery is a potential cause of postoperative bleeding. Miller et al. were the first group to describe hyperfibrinolysis using thromboelastogram (TEG) in the post-protamine period. In his series hyperfibrinolysis was uncommon (2 out 32 patients, 6.25%) and only present in the bigger patients (>8 kg cohort) (Miller et al. 1997, 2000).

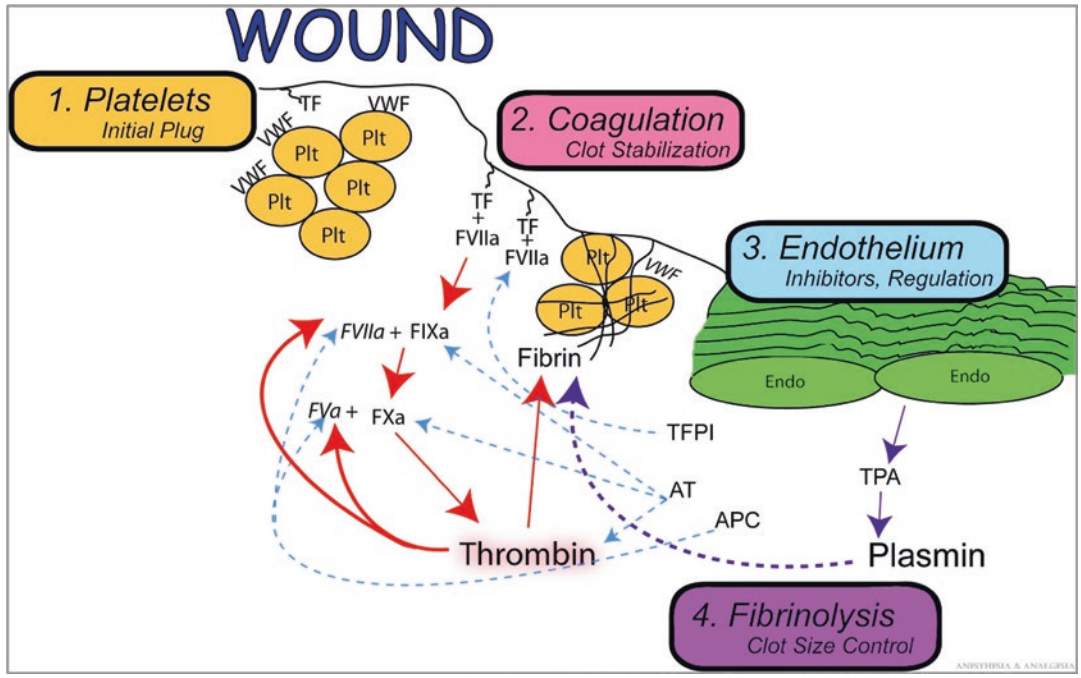

Fig. 2 Normal hemostasis. (*1*) Initial plug formation begins with von Willebrand factor (V.W.F.) binding to collagen in the wound and platelets (Plt) adhering to V.W.F. (*2*) Coagulation is initiated by small amounts of active factor VII (FVIIa) in blood binding to the exposed tissue factor (T.F.) in the wound, leading to activation of factor IX (FIXa) and factor X (FXa), which in turn initiates the conversion of prothrombin to thrombin. Thrombin creates a positive feedback loop by activating factors VIII (FVIIIa) and V (FVa), which increases FIXa and FXa's conversion of prothrombin to thrombin. This local burst of thrombin production at the wound site converts soluble fibrinogen into a fibrin mesh that stabilizes the initial plug. (*3*) Clot formation away from the site of injury is prevented by antithrombin (AT), which destroys thrombin and FXa, FIXa, and FXIa, activated protein C (A.P.C.), which destroys FVIIIa and FVa, and tissue factor pathway inhibitor (T.F.P.I.), which destroys TF-VIIa complexes. (*4*) Additionally, the endothelium (Endo) secretes tissue plasminogen activator (T.P.A.), which binds to fibrin and converts plasminogen to plasmin, which in turn lyses the fibrin. Once a stable clot is formed and the wounded tissue is no longer exposed, the regulatory proteins and fibrinolytic proteins prevent further thrombus formation. (Published with permission from Wolters Kluwer Health, Inc (Sniecinski and Chandler 2011))

Point-of-Care Testing and Algorithms in Postoperative Bleeding

A detailed description of the value of POC in postoperative bleeding is available in chapter "Khorgamielectrocardiography: Basic knowledge with focus on fetal and pediatric ECG". The value of ROTEM, TEG, and traditional preoperative testing in predicting bleeding after pediatric cardiac surgery is under investigation. POC algorithms have been used for the stepwise approach of postoperative bleeding which is also presented in chapter "Khorgamielectrocardiography: Basic Knowledge with Focus on Fetal and Pediatric ECG". The aim of POC algorithms is a targeted treatment of postoperative bleeding minimizing blood transfusion while improving surgical outcomes. Romlin et al. demonstrated that ROTEM. could be used early during the rewarming period of CPB before hemoconcentration accelerating the analysis by running the intrinsically activated thromboelastometric test (INTEM) clotting time (CT) with heparinase (HEPTEM) and the ROTEM channel to determine the function of fibrinogen (FIBTEM) receiving information of clot firmness after just 10 min (Romlin et al. 2013). The same Swedish group studied a pediat-

ric cardiac surgery population using TEG as POC testing showing decreased transfusion rate of PRBC and FFP while receiving more platelets and fibrinogen (Romlin et al. 2011). Other studies like the one by Lee et al. could not show that ROTEM predicted chest tube output after cardiac surgery (Lee et al. 2012).

Currently at Texas Children's in high-risk patients, we use ROTEM as POC running HEPTEM and FIBTEM upon rewarming of CPB following Romlin et al.'s approach. The more prevailing finding is the decrease in maximum clot firmness (MCF) in both tests (HEPTEM MCF <50 mm, FIBTEM <9 mm). We utilize a modified version of the Clinic Cologne–Merheim algorithm. (Fig. 3) (see section "Case Vignette") (Vorweg et al. 2001). Espinosa et al. showed that ROTEM and TEG parameters correlated well with post-CPB hemostasis changes and plasma fibrinogen and helped to guide fibrinogen replacement (Espinosa et al. 2014). Nakayama in pediatric cardiac surgical population validated the use of thromboelastometry-based algorithm reducing postoperative bleeding and decreasing the intensive care unit stay versus conventional treatment (ACT and platelet count transfusion guided) (Nakayama et al. 2015).

Machovec et al. describe the best approach to build a transfusion algorithm for pediatric cardiac surgery. The manuscript reviews to start by searching the best available evidence regarding bleeding risk factors, laboratory testing, target hemoglobin levels, and the indication for the use of blood components. Next, the authors highlight that the approach to the bleeding patient is better with the transfusion-guided algorithm than with non-algorithm management. Finally, the recommendation is that the algorithms be tailored to each induvial practice and not a universal approach to coagulopathy (Machovec and Jooste 2019).

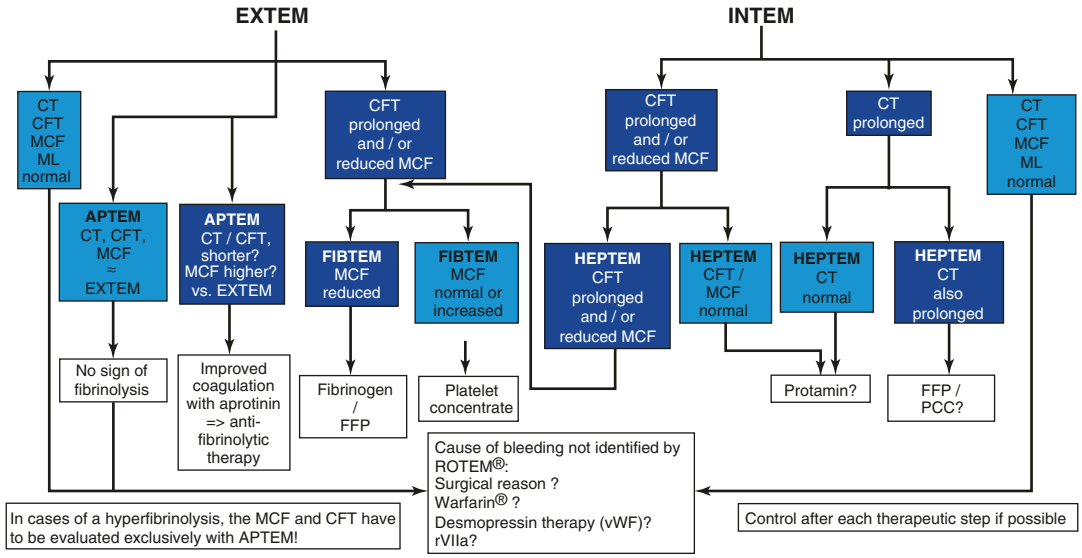

Fig. 3 Differential diagnostic and therapeutic ROTEM® algorithm used in the Clinic Cologne–Merheim (Vorweg et al. 2001)

Prophylaxis

Preoperative Optimization

It is important in the preoperative visit to review all active medications and its indications. As detailed before, antiplatelet agents should be discontinued 5–7 days before surgery unless the risk of thrombosis is extremely high (e.g., shunt-dependent lesion with low SaO_2). LMWH treatment can be continued in the preoperative period, but the last dose should be given subcutaneously 8–12 h before elective surgery. Vitamin-K antagonist should be stopped after overlapping treatment with UH as an inpatient and reaching a target APTT 1.5–2.5 normal values. Residual Coumadin effect should be ruled out on the day of surgery with a INR value. It usually takes 3–5 days to normalize the INR after stopping warfarin (Kozek-Langenecker et al. 2017; Tibi et al. 2021).

Sisti et al. showed that the acute warfarin reversal with prothrombin complex concentrate agent in pediatric patients with continuous-flow ventricular assist devices undergoing orthotopic heart transplantation was associated with less blood product exposure than those reversed with FFP (Sisti et al. 2020).

Herbal medications use is not as prevalent in children as in adults with a reported use of 3.5 versus 16%, respectively. Many of the herbal supplements such as garlic, ginkgo biloba, *Panax ginseng*, and/or ginger that can affect coagulation and should be stopped a week before surgery (Everett et al. 2005; Kaufman et al. 2002).

Cyanotic heart disease patients and especially those with hematocrit >65% are admitted to the hospital before surgery for preoperative hydration and to avoid triggering hyperviscosity syndrome with prolonged preoperative fasting. Intraoperative acute red cell reduction by replacing equal volume with plasma or albumin has shown to increase cardiac output and cerebral blood flow. In addition, platelet function and hemostasis will improve within a few hours of phlebotomy. Sahoo et al. showed that hemodilution to a hematocrit of 45% in patients with cyanotic heart disease undergoing Blalock–Taussig (BT) shunt decreases postoperative blood loss and increases shunt patency (Sahoo et al. 2007).

Intraoperative

General Measures

Control of surgical bleeding is crucial to stop triggering the coagulation cascade by the tissue factor and avoid coagulopathy consumption. Furthermore, the persistent bleeding factors should be corrected, for example, hypothermia, acidosis, electrolyte disturbance, and erythrocytosis. Even how rewarming is conducted is very important to avoid the temperature after-drop after weaning of CPB with core hypothermia. Saleh et al. showed that decreasing the temperature gradient between the heater–cooler unit and the patient core temperature to only 3 °C improved the hemodynamics, lowered the inotropic requirement, improved the hemostasis, and decreased the ICU stay (Saleh and Barr 2005).

During CPB heparin anticoagulation is used to decrease coagulation activation and to avoid thrombosis of the bypass circuit. The benefits of the use of heparin concentration-based systems (Hepcon H.M.S.; Medtronic, Minneapolis, MN) to titrate heparin effect are still debated in cardiac surgery. Guzzetta et al. showed that a heparin concentration-based system protocol in infants (<6 months) was associated with reduced activation of the hemostatic system decreasing postoperative blood loss and avoiding blood transfusion (Guzzetta et al. 2008). In an adult population, Ichikawa et al. showed that residual UH by Hepcon did not correlate with postoperative bleeding after cardiac surgery (Ichikawa et al. 2014). Protamine binds ionically to UH to reverse its effect. The adequate dosing of protamine is crucial because the incomplete reversal of UH will affect the patient hemostasis. On the other hand, excess protamine can lead to hypercoagulable state due to its inhibition of serine proteases debilitating the clot strength and clot kinetics and decreasing platelet aggregation. Again, the use of Hepcon monitoring for protamine titration is still controversial. Gautam

et al. recommended calculating protamine dosing with patient-estimated blood volume instead of dosing to the combined blood volume (pump + patient blood volume) to avoid prolongation of the initiation of the clotting time due to excess protamine (Gautam et al. 2013). Other strategies used to decrease the CPB activation of inflammatory and coagulation pathways are to limit cardiotomy suction, improve CPB circuit biocompatibility, supplement antithrombin III, and prophylactic use of antifibrinolytics.

Prophylactic Agents

Antifibrinolytics (Table 3)

The lysine analogs tranexamic acid (TXA) and ε-aminocaproic acid (EACA) are the commercially available antifibrinolytics in the United States. Current guidelines recommend using antifibrinolytics to reduce perioperative bleeding in medium to high-risk cardiovascular surgery. Comparative studies in children with cyanotic heart disease undergoing corrective surgery between TXA and EACA showed no difference in terms of reducing postoperative blood loss, as well as blood and blood product use (Chauhan et al. 2004; Martin et al. 2011a, b). In addition, in newborn surgery, EACA and TXA have been equally effective to prevent postoperative bleeding (Martin et al. 2011a, b).

The mechanism of action of lysine analogs is to bind competitively to the lysine-binding site on plasminogen, which inhibits the attachment of plasmin to fibrin, impeding the degradation of fibrin and fibrinolysis.

Large differences have been reported in the pharmacokinetics of antifibrinolytics between adults and children undergoing cardiac surgery on CPB especially in neonates due to their lack of renal and liver maturation. In addition, neonates suffer a massive hemodilution effect (50–100% of their blood volume), diluting the coagulation factors as well as the antifibrinolytic drug (Nilsson 1980; Ririe et al. 2002).

The pharmacokinetics of TXA is characterized by low protein binding (3%) and low volume of distribution (0.39 L/kg). The elimination half-life is 2 h and is eliminated unchanged by urinary excretion primarily via glomerular filtration. The therapeutic drug concentration for fibrinolysis inhibition is 10–20 μg/mL.

Traditionally dosing schemes derived from adult studies recommended 100 mg/kg over 15 min followed by a continuous infusion of 10 mg/kg/h, and 100 mg/kg was administered into the pump reservoir. Following concerns of increases in seizure activity, the TXA dosing has been decreased to 30 mg/kg load, 15 mg/kg/h infusion, and 2 mg/kg in the CPB prime (Murkin et al. 2010). Pharmacokinetic studies suggested

Table 3 Antifibrinolytics

Drug	MA	PK	Therapeutic concentration/dose	AE
Tranexamic acid	Inhibits the degradation of fibrinogen	*Protein binding* 3% V_d, 0.39 L/kg *Half-life*, 2 h *Excretion* renal via glomerular filtration (95% of unchanged)	20 μg/mL *Bolus dose* 6.4 mg/kg *Infusion* between 2.0 and 3.1 mg/kg/h (decrease infusion with increase weight)	Seizures Thrombosis
ε-Aminocaproic acid	Inhibits the degradation of fibrinogen	*Protein binding* V_d, 0.42 L/kg *Half-life*, 77 min *Excretion* renal via glomerular filtration	50–130 mg/L *Pediatric* *Bolus* 75 mg/kg over 10 min *Infusion* 75 mg/kg *Pump prime* 250 mg per 1 mL of prime *Neonates* *Bolus* 40 mg/kg *Infusion* of 30 mg/kg/h *Pump prime* 0.1 mg per 1 mL of prime	Thrombosis

MA mechanism of action, *PK* pharmacokinetics, *AE* adverse events

lower weight-adjusted dose to achieve a therapeutic concentration of 20 μg/kg. The recommended TXA bolus dose is 6.4 mg/kg followed by a continuous infusion between 2.0 and 3.1 mg/kg/h (infusion rate decreases with increasing weight) (Grassin-Delyle et al. 2013). Wesley et al. describe that the dosing requirements of TXA change rapidly during the first year of life, specifically, between 2 and 12 months of age. Younger patients require a higher loading dose (12 mg/kg) due to the increase in volume of distribution (Wesley et al. 2015).

Gertler et al. recommended maintaining the therapeutic concentration above 20 μg/mL a 10 mg/kg TXA bolus, an infusion of 10 mg/kg/h followed by 4 mg/kg CPB prime bolus. Once on CPB, the drip needs to be reduced to 4 mg/kg/h (Gertler et al. 2017).

High-dose TXA regimens in older patients undergoing CPB with open-chamber cardiac surgery have been associated with clinical seizures in susceptible patients. The proposed mechanisms for the seizures include decreased blood flow and inhibition of γ-aminobutyric acid A (GABA-A) receptors. The GABA-A receptors hyperpolarize the brain by increasing the chloride conductance through the receptor. TXA blocking the GABA-A receptor lowers the depolarization threshold and enhances excitotoxicity (Eaton et al. 2015).

The EACA has similar pharmacokinetics to TXA with no protein binding, volume of distribution (0.42 L/kg), and an elimination half-life of 77 min.

More than 80% is eliminated unchanged in the urine by glomerular filtration.

The therapeutic drug concentration for fibrinolysis inhibition is 50–130 mg/L.

Established EACA dosing in pediatric cardiovascular surgery is 75 mg/kg IV bolus followed by 75 mg/kg infusion and 15 mg/kg added to the pump prime. However, a recent study showed that EACA clearance is reduced in neonates undergoing elective cardiac surgery due to the decreased glomerular filtration rate compared with older patients. For this reason, the loading dose and infusion dose need to be decreased to about 50% of dose required in children and adults. Currently simulation studies recommend a priming dose of 0.1 mg EACA per 1 mL of blood prime, an IV loading dose of 40 mg/kg, with an infusion of 30 mg/kg/h. Using this dosing regimen maintained a steady-state concentration of 100 mg/L needed to prevent fibrinolysis (Eaton et al. 2015).

All antifibrinolytic therapy increases the risk of thrombosis with the use of TXA or EACA, so its administration is usually stopped once surgery is finished unless a pattern of hyperfibrinolysis is identified in the POC testing.

The serine protease inhibitor aprotinin is the most effective antifibrinolytic, but it was withdrawn from the US market due to safety concerns. Fergusson et al. in a multicentric randomized trail (BART study) comparing TXA, EACA, and aprotinin in high-risk cardiac surgery demonstrated that, even though it was the most effective drug to decrease the risk of massive bleeding, aprotinin increased the risk of mortality by 2.1%. The mortality is due to increased risk of cardiac death (cardiogenic shock, right ventricular failure, congestive heart failure, or myocardial infarction). In other studies, aprotinin has been linked with acute renal failure (Fergusson et al. 2008).

Treatment

The treatment of postoperative bleeding should be multimodal. On one hand should address the blood loss with PRBC replacement, but on the other hand ought to treat the coagulation disorder guided by POC testing. Massive blood transfusion is defined by the replacement of one or more circulating blood volumes. The estimated blood volume (EBV) decreases with age (Table 4). It is

Table 4 Estimated blood volume by age

Age	Estimated blood volume (mL/kg)
Premature infant	90–100
Term infant—3 months	80–90
Children >3 months	70

important in pediatric to calculate the maximal allowable blood loss (MABL):

$$\text{MABL} = \left(\text{starting Hct} - \text{lowest acceptable Hct}\right) / \text{starting Hct} \times \text{EBV}$$

The specific coagulation problem should be identified and addressed.

Abnormal Clot Generation

Abnormal clot generation is considered when the clotting time (CT) is prolonged in EXTEM (>90 s) and INTEM (>240 s).

Prothrombin Complex Concentrates (PCCs)

Prothrombin complex concentrates (PCCs) are the component of choice to treat abnormal clot generation and for reversal of oral anticoagulation before emergent cardiac surgery. PCCs are vitamin-K-dependent coagulation factors. In the United States, the PCC available is Kcentra® (C.S.L. Behring L.L.C., Kankakee, IL 60901) in which components are detailed in Table 5. The initial dose should be adjusted to the patients with INR. If the starting INR is between 2 and 4, the Kcentra® initial dose should be 25 IU/kg but not to exceed 2500. For INRs between 4 and 6, the initial dose should be 35 IU/kg, and for INRs >6 the initial dose should be 50 IU/kg. There is very limited published information in pediatrics with Kcentra®. Beaty et al. just published the initial experience at our center with Kcentra® (Beaty et al. 2016; Demeyere et al. 2010). Thromboembolic events have been reported with the repeated use of PCC. Recent Network for the Advancement of Patient Blood Management, Haemostasis and Thrombosis guidelines recommend against using PCCs post infant CPB unless used in the context of a randomized clinical trial (Faraoni et al. 2019b).

Table 5 Kcentra composition

Ingredient	Kcentra 500 units
Total protein	120–280 mg
Factor II	380–800 units
Factor VII	200–500 units
Factor IX	400–620 units
Factor X	500–1020 units
Protein C	420–820 units
Protein S	240–680 units
Heparin	8–40 units
Antithrombin III	4–30 units
Human albumin	40–80 mg
Sodium chloride	60–120 mg
Sodium citrate	40–80 mg
HCl	Small amounts
NaOH	Small amounts

Activated Factor VII

Activated recombinant factor VII (rFVIIa) is usually considered for patients with uncontrollable bleeding after pediatric cardiac surgery once other treatments have been used and failed. Okonta et al. reviewed the published experience with rFVIIa, which shows that it effectively decreases postoperative bleeding once other measures have failed. The recommended starting dose is 90 μg/kg; repeated doses might be given at 2-h (maximum of two doses). Thrombosis is the main complication reported, with an incidence of 4.2%. Patients on ECMO are at the highest risk for thrombosis. Thrombosis of the ECMO circuit has been reported. Lastly, Kcentra® contains 200–500 units of factor VII, so the use of rFVIIa should be avoided in these cases (Guzzetta et al. 2012; Okonta et al. 2012).

In a recent study by Downey et al., pediatric patients with post-CPB bleeding who received rFVIIa were more likely to develop thrombotic complications when compared with propensity-matched controls (Downey et al. 2017).

Abnormal Clot Stability

Abnormal clot stability is suspected when the ROTEM maximum lysis (ML) >15% of maximum clot firmness (MCF) in EXTEM (Fig. 4). Comparing EXTEM. with APTEM, results can be used to diagnose hyperfibrinolysis. APTEM test is an EXTEM assay in which fibrinolysis is inhibited by aprotinin. If the APTEM results improve the EXTEM, one hyperfibrinolysis should be considered and treated with antifibrinolytics.

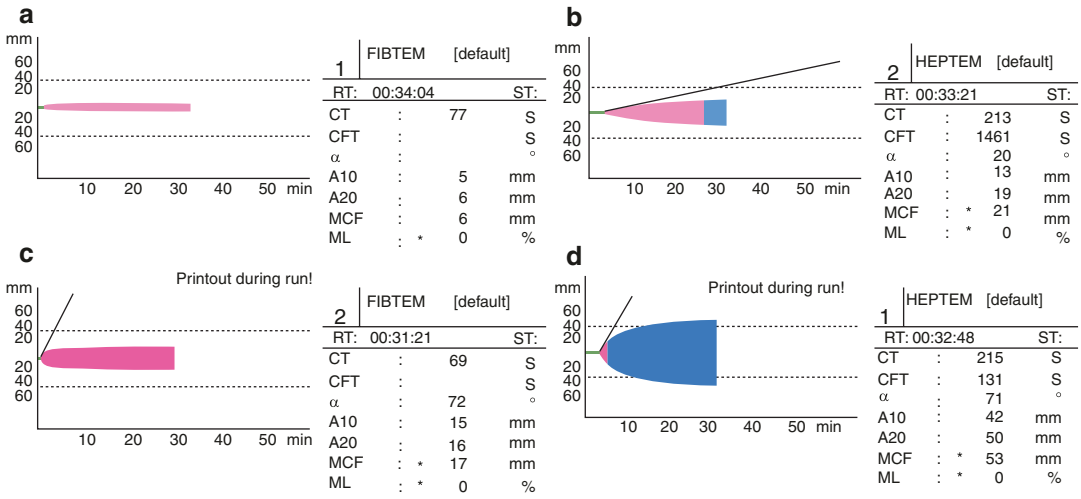

Fig. 4 (**a**, **b**) ROTEM tracing shows a decreased MCF in FIBTEM (<7–12 mm) and/or decreased M.C.F. in the HEPTEM (<50 mm). (**c**, **d**) The ROTEM tracing showed a FIBTEM MCF >17 mm and HEPTEM MCF >53 mm after the patient received 10 mL/kg of platelets and 70 mg/kg of fibrinogen concentrate. (RiaSTAPTM, C.S.L. Behring L.L.C., Kankakee, IL)

Antifibrinolytics

Antifibrinolytics are the agents of choice to treat hyperfibrinolysis diagnosed by a pattern of abnormal clot stability on EXTEM In high-risk cardiovascular surgery, antifibrinolytics are used as a prophylactic agent as described above. If they have not been used prophylactically and an ML >15% of MCF in EXTEM, either EACA or TXA should be started.

Clot Firmness

The clot firmness is affected when there is decreased concentration of fibrinogen, factor XIII, and/or platelets. The ROTEM tracing shows a decreased MCF in FIBTEM (<7–12 mm) and/or decreased MCF in the HEPTEM/EXTEM/INTEM (<50 mm). Since fibrinogen is an intravascular component and there is no tissue reservoir, is the first coagulation factor to drop after uncontrolled bleeding. There are two ways of replacing fibrinogen.

Fibrinogen Concentrate

Fibrinogen concentrate is obtained from human plasma by pasteurization and sterile filtration achieving a complete virus inactivation, which precludes viral disease transmission. Another advantage of fibrinogen concentrates in pediatric patients is the small volume required for its reconstitution avoiding volume overload complications (e.g., TACO or T.R.A.L.I.) and dilution of platelets and/or P.R.B.C. Galas et al. showed that fibrinogen concentrate is as effective as cryoprecipitate in postoperative bleeding after pediatric cardiac surgery (Galas et al. 2014). RiaSTAP® (C.S.L. Behring L.L.C. Kankakee, IL 60901) is commercially available in the United States. The recommended dose if the fibrinogen level is known is:

$$\text{Dose}\left(\text{mg}/\text{kg}\right)=\left[\text{Target Fib}\left(\text{mg}/\text{dL}\right)-\text{measured Fib}\left(\text{mg}/\text{dL}\right)\right]/1.7\left(\text{mg}/\text{dL per mg}/\text{kg}\right)$$

If the plasma concentration of fibrinogen is unknown, the starting dose is 70 mg/kg body weight.

Cryoprecipitate

Cryoprecipitate is the cold-insoluble white precipitate that forms when a unit of FFP thaws at 1–6 °C, and at room air has a very short half-life of 4 h. The unit of cryoprecipitate (5–15 mL) contains fibrinogen (150–700 mg), factor VIII (80–150 UI), von Willebrand factor (40–70% plasma concentration), factor XIII (30% of initial plasma concentration), and fibronectin (30–60 mg). In a cardiac surgery population, patients who received cryoprecipitate associated with FFP experience less bleeding than patients treated with FFP alone. The use of cryoprecipitate is associated with increased 5-year mortality in cardiac surgery, but it may be related to the severity of the bleeding. The dose used is variable. We start with 1 unit every 5 kg in our center in neonates and infants. Re-dosing only after fibrinogen levels or FIBTEM tracing are checked. Since fibrinogen concentrates became available, cryoprecipitate is the second-line treatment of postoperative bleeding due to hypofibrinogenemia secondary to the adverse event risks (e.g., transmission blood-borne pathogen, TACO, and TRALI) (Görlinger et al. 2013; Nascimento et al. 2014) (Lee et al. 2021).

Platelets

Platelets are prepared from the platelet-rich plasma component by apheresis. The platelets come from either a single or random donor platelet. Platelets have a short shelf life of only 4 days since they are stored at room temperature (20–24 °C) with continuous agitation to avoid aggregation. Due to this issue, platelets have the highest rate of bacterial contamination. Therefore, the recommendation is to use compatible recipients and donors in infants and children. Although irradiation kills viable lymphocytes, we indicate platelet transfusion when POC testing shows a decreased MCF in the HEPTEM/EXTEM/INTEM (<50 mm) with MCF in the FIBTEM channel in the normal range. Platelet count after cardiac surgery is an unreliable trigger for transfusion since platelets tend to clump in the post-hypothermic CPB period. In infants and neonates, we dose 1 unit every 5 kg of body weight. However, the administration of platelets is not devoid of complications, and adult studies have shown an association between platelet transfusion and TRALI and ischemic events.

Gautam et al. examined whether transfusing platelets during the rewarming phase could improve postoperative outcomes in a randomized controlled trial. The authors found that patients in the early platelet administration received 40% fewer post CPB blood products than the control group (Gautam et al. 2020).

Recent evidence in complex adult cardiothoracic surgery showed that platelets could be stored cold for up to 14 days. The results (e.g., total blood usage, number of adverse events, length of stay in intensive care, and mortality) were comparable with platelets stored at room temperature (Strandenes et al. 2020). Pediatric studies with cold platelets use are currently undergoing.

Fresh Frozen Plasma

Fresh frozen plasma is prepared from the platelet-rich plasma component of whole blood or apheresis and contains anti-ABO antibodies and stored at −18 °C or cooler. Factors V and VIII activity diminishes after 24 h. The freezing process kills the leukocytes, and further irradiation is not needed. FFP is thawed in a water bath at 30–37 °C for approximately 20–30 min before transfusion. Similarly, to PRBC patients can only receive plasma with anti-ABO antibodies that will not react with the patient's ABO surface antigens. Currently, FFP is used if individual components are not available for prolonged CT in EXTEM (>90 s) and INTEM (>240 s) and oral anticoagulant reversal. The starting dose is 5–10 mL/kg, but often higher doses are needed to achieve hemostasis. FFP volumes >15 mL/kg are associated with TACO, TRALI, sepsis, and nosocomial infections (Khan et al. 2007; Sarani et al. 2008).

We only use FFP in CPB prime in neonates and infants under 7 kg. As described before, FFP in CPB prime is not better than crystalloids in patients bigger than 7 kg (Dieu et al. 2020).

Packed Red Blood Cells

Packed red blood cells are necessary to increase the blood's oxygen-carrying capacity and increase end-organ perfusion. The threshold for transfusion depends on age, weight, physiology (cyanotic vs. acyanotic), ongoing blood loss, and adequacy of oxygenation/perfusion. PRBC transfusion is indicated if the hemoglobin concentration is <7 g/dL in acyanotic patients. However, the threshold for transfusion can be higher in premature, cyanosis, or chronic conditions (Guzzetta 2011). The physiologic nadir for hemoglobin occurs at approximately 2–3 months of age. The use of somatic and cerebral oximetry can guide transfusion in critical patients. Leukocyte reduction is used to decrease febrile nonhemolytic transfusion reactions, alloimmunization of recipients, and cytomegalovirus (CMV) transmission. The evidence is inconclusive (Simancas-Racines et al. 2015). PRBC stores at 1–6 °C in the anticoagulant/preservative solution citrate, phosphate, dextrose, adenine-formula 1 (CPDA-1). The hematocrit on PRBC is 65–80%, with a shelf life of 35 days. Irradiation is used to prevent transfusion-associated graft-versus-host disease in immunocompromised patients or transplant candidates but decreases shelf life (28 days). The target hematocrit on bypass is a debatable issue. No difference in outcomes has been seen between 25 and 35% hematocrits during CPB for pediatric congenital heart surgery in blood product use, psychomotor development, and imaging (Newburger et al. 2008). Before going on CPB is important to calculate the predicted hematocrit change (ΔHtc), and the PRBC need to achieve a desired hematocrit on CBP with the following formulas:

$$\Delta \mathrm{Htc} = \mathrm{Htc}_{\mathrm{pt}} \times \mathrm{Pt}_{\mathrm{BV}} / \mathrm{Pt}_{\mathrm{BV}} + \mathrm{CPB}_{\mathrm{PB}}$$

$$\mathrm{PRBC}(\mathrm{mL}) = \left[\mathrm{Htc}_{\mathrm{CPB}} \times \left(\mathrm{Pt}_{\mathrm{BV}} + \mathrm{CPB}_{\mathrm{PB}} \right) - \left(\mathrm{Pt}_{\mathrm{BV}} \times \mathrm{Htc}_{\mathrm{pt}} \right) \right] / 60\%$$

where Pt_{BV} is patient blood volume, CPB_{PB} is priming volume, PRBC is packed red blood cells, Htc_{pt} is patient hematocrit, and Htc_{CPB} is the hematocrit on the prime.

The use of umbilical cord blood for autologous transfusion in neonatal open-heart surgery has been described in detail by Fernandez et al. (Fernandez and Chasovskyi 2020). An early approach of arterial switch operation in conjunction with umbilical cord blood for autologous transfusion decreases homologous blood cell transfusion with similar outcomes to the conventional process (Chasovskyi et al. 2017).

Blood conservation strategies along and institutions protocols for hemostasis management can decrease the need of perioperative blood transfusion (Sebastian and Ahmed 2021).

Adverse Effects (Table 6)

Transfusion-related acute lung injury (TRALI) is characterized by non-cardiogenic pulmonary edema and severe hypoxia. The treatment is symptomatic with supporting measures, including mechanical ventilation. TRALI is the most common transfusion-related cause of death. There is a two-hit hypothesis for TRALI. First, are transfused neutrophils activating the endothelial cell in the lung, followed by the second hit, an overwhelming inflammatory response, capillary leakage, and pulmonary edema. Transfusion circulatory overload (TACO) is the second leading cause of transfusion-related death. TACO is considered acute pulmonary edema during or shortly after transfusion and is associated with symp-

Table 6 Transfusion complications

Metabolic	Hypocalcemia and hypomagnesemia (e.g., citrate toxicity) Hyperkalemia secondary to P.R.B.C. leakage: worse in old (>7 days) and irradiated blood Hypothermia Acidosis due to P.R.B.C. shift to anaerobic metabolism increasing lactic acid Shifts in the oxygen–hemoglobin dissociation curve
Infectious	Decreased by screening tests but not zero due to false-negative screen Hepatitis A, B, and C H.I.V. Human T lymphotropic virus I and II
Immune mediated	Incompatibility: Clerical error while checking blood products *Graft*-versus-*host disease* is caused by lymphocytes contained in a transfused blood component proliferate and causes host tissue destruction Hemolytic transfusion reactions Febrile nonhemolytic transfusion reactions Allergic reactions Transfusion-related acute lung injury Post-transfusion purpura Transfusion-related immunomodulation Alloimmunization

toms and signs of congestive cardiac failure. In addition, TACO is related to elevated B-type natriuretic peptides due to chamber distension (Iyengar et al. 2013; Toy et al. 2012).

Hemolytic transfusion reactions is the immunologic incompatibility between a transfusion recipient and the PRBC. There are two types of presentations acute (<24 h) or delayed (1–2 weeks after transfusion). The clinical presentation is characterized by fever, flank pain, and dark urine. The severity varies from mild to severe (e.g., intravascular hemolysis, disseminated intravascular coagulation, and distributive shock) (Strobel 2008).

Outcome

Guzzetta et al. showed that neonates who bleed more (upper quartile) post-cardiac surgery on CPB had a statistically significant increased risk of postoperative dialysis and ECMO support (Guzzetta 2011). In addition, neonates who had higher incidence of postoperative bleeding had longer hospital stay were at a higher risk for in-hospital mortality. Wolf et al. demonstrated that early postoperative bleeding was independently associated with an increased mortality, postoperative mechanical ventilation, and intensive care unit stay in infants after cardiac surgery (Wolf et al. 2014).

Bercovitz et al. presented evidence that excessive bleeding is associated with worse outcomes including longer length of stay or bigger risk of unplanned readmission (Bercovitz et al. 2018).

Case Vignette

A 6-month-old boy (6.5 kg/66 cm) presented with a past medical history of dextrocardia, double-inlet left ventricle, ventricular septal defect, subpulmonic stenosis, and right ventricular hypoplasia. He was palliated as a newborn with a modified right BT shunt (3.5 mm), and he was receiving aspirin until the day of surgery. In addition to his cardiac condition, the patient carries sickle cell trait with hemoglobin (Hb) S of 39%. Currently, the patient is experiencing desaturation (SaO_2 low 70 s) due to outgrowth of the BT shunt and is scheduled for bidirectional cavo-pulmonary shunt (Glenn shunt), and pulmonary valve oversaw on CPB. Therefore, the CPB prime volume for this size patient is 350 mL, and the estimated patient's blood volume is ~500 mL. To avoid a sickle cell crisis while on CPB, an exchange transfusion was performed on CPB initiation (Table 7). Therefore, the total prime volume ~ 900 mL was set to match the prime circuit volume and the patient's estimated blood volume.

Due to complex anatomy, the repair was long, with a CPB duration of 294 min and a cross-

Table 7 CPB prime for exchange transfusion

PRBC	595 mL
FFP	335 mL
Heparin	3500 U
$NaHCO_3$	20 mEq
$CaCl_2$	500 mg
EACA	420 mg

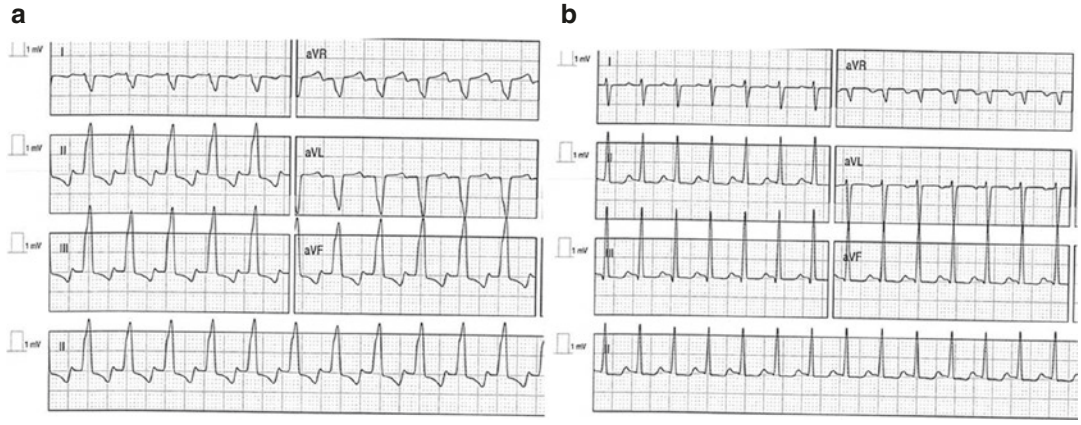

Fig. 5 (**a**) EKG trace showing a wide complex tachycardia secondary to hyperkalemia ($K = 6.5$ mEq/L) due to the multiple P.R.B.C. use. (**b**) EKG trace normalized after the potassium dropped to 5.2 mEq/L due to 15 min P.R.B.C. washing and increasing ionized Ca to 1.3 mEq/L

clamp time of 146 min. In addition to the prime blood products, two additional PRBC and one unit of FFP were administered during CPB. The patient has several risk factors for postoperative bleeding, including size, weight, cyanotic heart disease with single-ventricle physiology, aspirin until the day of surgery, Glenn shunt surgery, long cardiopulmonary bypass, and a complete exchange transfusion. POC testing with ROTEM was used, showing a decreased MCF in the FIBTEM y HEPTEM (Fig. 4a, b). This POC testing finding was consistent with the clinical scenario in which the patient removed the platelets from the circulation due to the complete exchange transfusion, and the fibrinogen was remarkably hemodiluted. Following our institutional POC, ROTEM-guided transfusion protocol recommended the administration of platelets and fibrinogen (Fig. 4)**.** Once the aorta was unclamped, the EKG showed a wide complex tachycardia probably secondary to hyperkalemia ($K = 6.5$ mEq/L) due to the multiple PRBC use (Fig. 5a). After 15 min of washing the PRBC and increasing the ionized Ca to 1.3 mEq/L, the potassium dropped to 5.2 mEq/L and the EKG normalized (Fig. 5b). However, there was still profuse bleeding from the suture lines once the patient was weaned off CPB, and heparin was reversed with protamine achieving a baseline ACT. The patient received 10 mL/kg of platelets and 70 mL/kg of fibrinogen concentrate (RiaSTAP, C.S.L. Behring L.L.C., Kankakee, IL) with a remarkable clinical response. The ROTEM tracing showed a FIBTEM MCF >17 mm and HEPTEM MCF >53 mm (Fig. 4c, d). The patient was admitted to the ICU and weaned off the ventilator the next day. He did not present with any further bleeding problems.

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Postoperative Central Nervous System Management in Patients with Congenital Heart Disease

Ali Dabbagh and Michael A. E. Ramsay

Abstract

The mortality rate of neonates and children with congenital heart disease (CHD) has decreased during the last decade. However, emerging concerns have increased regarding the neurologic and neurodevelopmental outcomes. Various studies have quoted different results for the rate of neurologic injuries: even as high as 70%. CHD is by itself a risk factor for an increased chance of neurologic injuries; brain injuries are found in about one-third of full-term neonates who have underlying CHD. Risk factors for central nervous system (CNS) injury in neonates and infants undergoing cardiac surgery are discussed in this chapter in three main classes: preoperative, intraoperative, and postoperative risk factors. Also, classification of CNS deficits is considered under these main categories: neurologic deficits, neurocognitive and neurodevelopmental disorders, and white matter injuries (WMI), including Periventricular leukomalacia (PVL). Besides, postoperative delirium is presented at the end of the chapter.

Keywords

Postoperative care · Central nervous system management · Congenital heart disease · Neurocognitive disorders · Neurodevelopmental disorders · White matter injuries · Periventricular leukomalacia · Delirium

The Impact of CNS Outcome in Pediatric Cardiac Surgery

The mortality rate of neonates and children with congenital heart disease (CHD) has decreased during the last decade due to advanced techniques of care especially perioperative surgical, anesthetic, and intensive care, in addition to the development of new drugs and novel techniques. However, emerging concerns have increased regarding the neurologic and neurodevelopmental outcomes of these patients with a broad list of etiologies and multifactorial risk factors. Various studies have quoted different results for the rate of neurologic injuries, even as high as 70% in some studies (van Tilborg et al. 2016; Wernovsky and Licht 2016; Graham et al. 2019; Verrall et al. 2019).

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Growing evidence suggests that CHD is by itself a risk factor for an increased chance of neurologic injuries; brain injuries are found in about one-third of full-term neonates who have underlying CHD. The heart develops early during gestation, and any congenital impairment in the development of the cardiovascular system profoundly affects neural development, leading to brain immaturity even in term infants with underlying CHD (Barkhuizen et al. 2021). Congenital heart disease has a profound effect on fetal brain development for the remainder of gestation; even term infants with critical CHD are born while being highly susceptible to hypoxic-ischemic injuries (Verrall et al. 2019). However, other neonates and infants with CHD are much more vulnerable to global hypoxic-ischemic insult and white matter injuries (WMI) including periventricular leukomalacia (PVL). Besides the innate vulnerability of the developing brain to any insult, there are a multitude of perioperative risk factors and perioperative events that increase the chance of brain injuries in this patient population and are discussed in the next section (Wernovsky and Licht 2016; Graham et al. 2019; Verrall et al. 2019).

Risk Factors for CNS Injury in Neonates and Infants Undergoing Cardiac Surgery

Neonates and infants undergoing cardiac surgery are at increased risk of central nervus system (CNS) injury before the surgical procedure; in fact, many studies have demonstrated inherent genetic and/or developmental risk factors in association with CHD (Edwards and Gelb 2016; Pierpont et al. 2018; Verrall et al. 2019; Yasuhara and Garg 2021).

The perioperative period imposes an additional burden on these patients which affects the outcome. Some risk factors are modifiable, while other risk factors have limited options.

Many studies have been performed to assess the impact of different risk factors on the occurrence of CNS injuries in patients with congenital heart disease undergoing surgery, including a relatively large number of primary studies and an acceptable number of reviews. These risk factors may be categorized according to a time-based schedule; however, these are "personalized factors" that are matched individually for each patient, while they are "likely interrelated, cumulative and synergistic" with a development "throughout fetal life to childhood" (Williams and Ramamoorthy 2007; Harbison et al. 2017; Morton et al. 2017; Howell et al. 2019; Costerus et al. 2020; Finucane et al. 2020):

- Preoperative risk factors (from the fetal period up to the time of operation),
- Intraoperative risk factors (i.e., throughout the time of operation),
- Postoperative risk factors (i.e., during the postoperative period which is after the termination of surgery and patient transfer to cardiac intensive care unit [ICU]).

Preoperative Risk Factors for CNS Injuries in Neonates and Children

The main preoperative risk factors are summarized in Table 1. For the purposes of this discussion, we have denoted the "intrinsic" and "neonatal" risk factors under the category of "preoperative" risk factors. In patients undergoing perioperative care for congenital cardiac surgery, the majority of these risk factors are not modifiable, while only some are modifiable. However, all should be recognized in order to manage, or at least estimate the patient risk in the perioperative period (Hsia and Gruber 2006; McQuillen et al. 2007; Lee et al. 2008; Massaro et al. 2008; Albers et al. 2010; Harbison et al. 2017; Morton et al. 2017; Pierpont et al. 2018; Howell et al. 2019; Yasuhara and Garg 2021).

Intraoperative Risk Factors for CNS Injuries in Neonates and Children

The main intraoperative risk factors can mainly be categorized under cardiopulmonary bypass

Table 1 Preoperative risk factors affecting CNS outcome in neonatal and pediatric congenital heart surgery

Risk factor	Relationship with CNS disorders
Genetic risk factors	• Genetic syndromes have significant detrimental effects on CNS outcome,
	• Trisomy 21, DiGeorge, conotruncal anomalies, VACTERL, and velocardiofacial syndrome (Atallah et al. 2007; Gaynor et al. 2007; Lee et al. 2008; Kaltman et al. 2010; Chung et al. 2015; Edwards and Gelb 2016; Pierpont et al. 2018; Yasuhara and Garg 2021)
	• Most of the above genetic syndromes have a common genetic abnormality—22q11 chromosome deletion (Goldmuntz 2005)
	• In neonates with 22q11.2 deletion syndrome, the chance for congenital heart disease is about 80% (Momma 2010)
	• Carotti et al. described some conotruncal anomalies associated with 22q11 deletion syndrome: "*Tetralogy of Fallot, pulmonary atresia with ventricular septal defect, truncus arteriosus, interrupted aortic arch, isolated anomalies of the aortic arch, and ventricular septal defect*" which are usually associated with other "*anomalies of the aortic arch, pulmonary arteries, infundibular septum, and semilunar valves*" (Carotti et al. 2008).
	• Other genetic syndromes that are associated with developmental delay in children with congenital heart disease are Alagille, CHARGE, Down, Jacobsen, Noonan, Turner, Williams (Marino et al. 2012; Yasuhara and Garg 2021).
	• Genetic vulnerability, genetic predisposition, and perioperative genomics affect CNS outcome in patients undergoing congenital heart surgery; e.g., ***APO-E allele polymorphisms*** are associated with an increased chance of CNS disorders (Gaynor et al. 2003, 2007; Marino et al. 2012; Morton et al. 2017).
Impaired development of CNS in utero	Antenatal administration of the following could help prevent in utero CNS injuries especially for the protection of oligodendrocytes:
	• free radical scavengers including vitamin E
	• anti-inflammatory and/or anti-cytokine agents to decrease the chance of fetal/maternal inflammation
	• antibiotics to decrease the chance of infection (Volpe 2001; Rezaie and Dean 2002; Lee et al. 2008; Licht et al. 2009; Thomason 2020).
Congenital structural CNS malformations and/or acquired CNS disorders or injuries in utero or during the perioperative period	There is an increased chance of congenital structural CNS disorders in patients with CHD.
	• **Cerebral dysgenesis** has a wide spectrum from microdysgenesis to major anatomical congenital defects like corpus callosum agenesis, white matter injury, microcephaly, and incomplete operculization; also, "hypotonia, seizures, feeding difficulties, and brain imaging abnormalities like stroke, hemorrhage, or periventricular leukomalacia" are among the lesions in these patients (Newburger and Bellinger 2006; Licht et al. 2009; Rollins and Newburger 2014; Morton et al. 2017; Barkhuizen et al. 2021).
Antenatal hemodynamic instability and/or preoperative hemodynamic instability including preoperative hypoxia or severe acidosis	• Before birth, impaired fetal blood flow and the resulting decrease in brain oxygen delivery are the main sources of brain insults (Licht et al. 2009; Kaltman et al. 2010).
	• After birth, decreased or impaired oxygen delivery to the brain results in injuries to the CNS especially the white matter or those regions communicating different parts of the brain (Kaltman et al. 2010).
	• Cardiac arrest and cardiopulmonary resuscitation are both associated with increased risk of worse neurologic and/or neurodevelopmental outcomes, either before birth or during the preoperative period (Marino et al. 2012; Rollins and Newburger 2014; Morton et al. 2017).
Preoperative hyperthermia	• Even mild hyperthermia in ischemic CNS regions may have considerable and significant impact on CNS status.
	• These deleterious effects should especially be avoided in patients undergoing DHCA; CNS tissue is highly sensitive to ischemia and temperature changes especially during the pre-bypass period and early post-bypass (Shum-Tim et al. 1998; Nussmeier 2005; Shamsuddin et al. 2015; Hu et al. 2016).
Preoperative hypoglycemia	• Tight control of blood glucose is controversial, however, profound hypoglycemia or hyperglycemia should be avoided (Hirsch et al. 2012).

(continued)

Table 1 (continued)

Risk factor	Relationship with CNS disorders
Prematurity	• Congenital heart disease patients with prematurity (<37 weeks, especially those weighing less than 1500 g at birth) is also associated with high risk for developmental delays and/or disorders (Marino et al. 2012; Rollins and Newburger 2014).
	• Despite great improvements in the care of the neonates in NICU's, about 5–10% of premature neonates have major motor deficits; while more than 50% have significant impairments in behavioral, cognitive or sensory fields (Khalil et al. 2014; Back 2015; Li et al. 2015)
Low birth weight	• LBW is an important risk factor because it could be the result of many other independent risk factors including "**prematurity, associated genetic syndromes, placental insufficiency, and intrauterine growth restriction**" (Gaynor et al. 2007; Lee et al. 2008)
Perinatal asphyxia and/or cardiorespiratory problems in perinatal period	• Increase the chance of perinatal hypoxic-ischemic insult to the brain; with resultant sequelae (Gaynor et al. 2007; Lee et al. 2008; Popescu et al. 2020)
Trauma during birth	• Increases the chance for cerebral hemorrhage and/or hypoxic-ischemic insults; which could be possibly a potential source for CNS injuries (Kelly et al. 2014; Li et al. 2015)
Age at the time of surgery	Early corrective surgery vs. late correction is still controversial.
	• Early correction has been associated with improved cardiac outcomes.
	• CNS plasticity in neonates may compensate for the effects of cardiopulmonary bypass (CPB).
	• Later correction may favor improved CNS outcome and preventing untoward effects of CPB on CNS; controversy still exists (Kaltman et al. 2010; Barron 2013)
Preoperative treatments	• Treatments like balloon atrial septostomy are associated with increased risk of stroke in the preoperative period. (Of note, some studies have not confirmed this association McQuillen et al. 2006; Lee et al. 2008; Beca et al. 2009).
Underlying cardiac lesion	• Some specific preoperative cardiac disorders are associated with increased risk of postoperative CNS lesions:
	• Single ventricle anatomy, d-transposition of the great arteries, and Tetralogy of Fallot (Mahle et al. 2002; Bellinger et al. 2011, 2015a, b; Goldberg et al. 2014; Dehaes et al. 2015)
Mechanical support/heart transplantation	• Patients receiving mechanical support both in the preoperative period or during postoperative care (either as Extracorporeal Membrane Oxygenation or Ventricular Assist Devices) are at risk of hemodynamic instability; besides, they are at increased risk of thromboembolic events; on the other hand, patients with heart transplantation are at increased risk for worse CNS outcome (Massaro et al. 2008; Marino et al. 2012; Rollins and Newburger 2014)

(CPB)-related factors (Table 2); however, intraoperative risk factors are not just limited to this (Table 2) (Shen et al. 2003; Hsia and Gruber 2006; Lee et al. 2008; Massaro et al. 2008; Albers et al. 2010; Kaltman et al. 2010; Dabbagh et al. 2012).

Postoperative Risk Factors for CNS Injuries in Neonates and Children

During the **postoperative** period, some important events occur. First of all, the aftermath of surgical trauma, with all of its inflammatory events, affects different organ systems including the CNS. Second, factors like "impaired autoregulation, unstable hemodynamics, hyperthermia after cardiopulmonary bypass, pain, and vanished effects of anesthetic drugs leading to arousal after anesthesia" superimpose the potential underlying factors which may lead to unwanted CNS complications. The main **postoperative risk factors** are categorized in Table 3 (Hsia and Gruber 2006; Lee et al. 2008; Massaro et al. 2008; Albers et al. 2010; Kaltman et al. 2010; Morton et al. 2017; Howell et al. 2019).

Table 2 Intraoperative and Cardiopulmonary Bypass (CPB) related factors affecting CNS outcome in neonatal and pediatric congenital heart surgery

Potential risks	How to prevent or compensate
Gaseous microemboli	• Using arterial filters (at least 40 μ; smaller 20 μ filters are superior); using microporous hollow fiber oxygenators.
	• Debubbling the oxygenator before CPB with extreme accuracy and vigilance (Matte et al. 2016; Zhu et al. 2020)
Macroemboli and particles (especially clots); low levels of antithrombin III	• Ensuring enough dose of heparin for anticoagulation before the establishment of CPB; using fresh frozen plasma (FFP) in prime volume to compensate for lower levels of antithrombin III, which is common especially in neonates and infants less than 6 months of age.
	• Antithrombin III supplementation is much more efficacious than FFP (Codispoti et al. 2001; Kaltman et al. 2010; Campello et al. 2016)
Inflammation due to CPB circuit	Several anti-inflammatory strategies have been suggested in many studies, to be used during CPB:
	• Steroids (especially methylprednisolone)
	• Heparin-coated circuits
	• Leukocyte filtration strategies
	• Ischemic preconditioning models for the brain
	• Institution of modified ultrafiltration
	• Of note, none have been proved as a definite therapy (Shen et al. 2003; Ungerleider and Shen 2003; Lee et al. 2008; Kaltman et al. 2010)
Potential episodes of systemic hypotension or hypoperfusion during CPB	• Appropriate monitoring
	• Administering higher flow during CPB than "full flow bypass" (Shamsuddin et al. 2015)
Hemodilution during Cardiopulmonary Bypass (CPB)	Avoid extreme hemodilution during CPB with different methods:
	• Priming part of the circuit with RBC's, managing cardioplegia, and using minimum volume circuits.
	• It has been recommended to adjust hematocrit levels with CPB temperature (in Celsius); however, strong evidence recommends strict avoidance of hematocrit levels below 24% (Ungerleider and Shen 2003; Durandy 2010; Kaltman et al. 2010; Hirsch et al. 2012)
DHCA (Deep Hypothermic Circulatory Arrest)	• DHCA is a real risk especially when prolonged more than 45 min; administering antegrade cerebral perfusion or regional low flow cerebral perfusion (Gaynor et al. 2007; Kaltman et al. 2010)
	• Alternative neuroprotective strategies like Antegrade Cerebral Perfusion (ACP) have been used for CNS preservation; however, Regional Cerebral Perfusion (RCP) has not been much in favor of improved outcomes (Fraser and Andropoulos 2008; Nelson et al. 2008; Ohye et al. 2009; Kaltman et al. 2010)
	• At least 20 min of cooling should be allowed to have appropriate cerebral cooling before DHCA (Hsia and Gruber 2006)
	• Using packed ice around the head during DHCA (Hsia and Gruber 2006; O'Neill et al. 2012)
Rate and duration of core cooling; pH management during core cooling	• Most clinicians have shifted to pH-stat strategy especially when using DHCA (Hsia and Gruber 2006; Abdul Aziz and Meduoye 2010; Ismail and Semien 2021)
Air trapping and air emboli after cardiac chambers are opened	• Preventing air ejection into the arterial system after removal of the aortic cross-clamp by the surgeon; if air bubbling occurs, re-establishment of CPB and other measures like hyperbaric oxygen therapy could be useful
Impaired cerebral perfusion; hemodynamic perturbations of cerebral blood flow (CBF)	• Ensuring adequate cerebral perfusion pressure (CPP) and cerebral blood flow (CBF) during CPB
	• Preventing hypotension during CPB
	• Avoiding hemoglobin drop
	• Checking CPB circuit for the proper and appropriate size of arterial and venous cannulae; sufficient setting of the CPB reservoir and venous cannulae to ensure venous drainage (Dehaes et al. 2015; Ismail and Semien 2021; Li et al. 2021)

(continued)

Table 2 (continued)

Potential risks	How to prevent or compensate
Oxidative stress of the Central Nervous System	• Anti-oxidative measurements
	• Normoxic management and avoidance of hyperoxia and controlled re-oxygenation during CPB especially in cyanotic patients
	• Monitoring with F(2)-isoprostanes (F(2)-IsoPs), neuron-specific enolase (NSE), S-100 Beta, C-reactive protein (Arneson and Roberts 2007; Williams and Ramamoorthy 2007; Kaltman et al. 2010; Morita 2012; Cardenas-Rodriguez et al. 2013; Kochanek et al. 2013; Caputo et al. 2014; Pierpont et al. 2018)
Anesthetic drugs	• There is a great amount of concern in favor of anesthetic neurotoxicity in animal models of developing brain.
	• Clinically there is still controversy without decisive results and those studies performed in humans have failed to confirm these studies in human pediatric and neonatal anesthesia (McCann and Soriano 2012; Vutskits 2012; Zhou and Ma 2014; Hansen 2015; Morton et al. 2017; Howell et al. 2019)

Table 3 Postoperative risk factors affecting CNS outcome in neonatal and pediatric congenital heart surgery

Risk factor	How to prevent or compensate
Impaired CNS autoregulation	• Hemodynamic stability and prevention of hypotension
	• Ensuring adequate CNS oxygen delivery
	• Prevention of low hematocrit levels
	• Ensuring adequate ventilation and oxygenation
Clinical seizure and/or electroencephalographic (EEG) seizure (i.e., non-convulsive seizure)	• Continuous EEG monitoring; especially for patients at risk of seizure or with underlying CNS disorders; if a seizure starts from the frontal lobe, a worse "Psychomotor Developmental Index" is predicted in patients under 1 year
Postoperative hyperthermia	• Even mild degrees of hyperthermia in ischemic CNS regions could have considerable and significant impacts on CNS status; these deleterious effects should especially be avoided in patients undergoing DHCA; CNS tissue is highly sensitive to ischemia and temperature changes especially during the pre-bypass period and early post-bypass (Shum-Tim et al. 1998; Nussmeier 2005; Shamsuddin et al. 2015; Hu et al. 2016).
Postoperative arterial and/or venous desaturation	• Optimizing oxygenation, ventilation, hemodynamics, and hematocrit level prevents systemic desaturation; residual shunts or single ventricle anatomy affect significantly the level of postoperative saturation; systemic venous desaturation is an important indicator of decreased systemic oxygen delivery; postoperative monitoring with both "cerebral NIRS" and "somatic NIRS" could be a useful guide to foresee this event.
Single ventricle anatomy	• Increases the risk of arterial hypoxemia
	• Increased chance for systemic emboli;
	• Respiratory maneuvers, including preventing hyperventilation and hypocapnia and stable hemodynamics could help decrease the risk.
	• Cerebral and somatic NIRS could be of use (Dehaes et al. 2015). Goldberg et al. demonstrated impaired neurodevelopmental state in children with single right-ventricle anatomy at 3 years of age (Goldberg et al. 2014)
Increased Intracranial Pressure (ICP)	• Increased ICP leads to decreased cerebral perfusion pressure; head elevation and other maneuvers for prevention of ICP increase should be used.
Low Cardiac Output State (LCOS)	• LCOS is predicted to occur 6–18 h after surgery and occurs in 25% of infants and neonates undergoing congenital heart surgery.
	• Residual defects like hypoplastic left heart syndrome are associated with an increased chance of LCOS and hemodynamic support with pharmacologic agents (including, but not limited to milrinone, dobutamine, and levosimendan) could be used to treat LCOS.
Role of oxidative stress on CNS injury and refractory seizure	• Anti-oxidative measurements; normoxic management and avoidance of hyperoxia during CPB especially in cyanotic patients; monitoring with F(2)-isoprostanes (F(2)-IsoPs), neuron-specific enolase (NSE), S-100 Beta, C-reactive protein (Morita 2012; Cardenas-Rodriguez et al. 2013; Kochanek et al. 2013).

Table 3 (continued)

Risk factor	How to prevent or compensate
ICU Length-of-Stay	• Increased ICU stay associated with a higher chance of Intelligent Quotient (IQ) drop (Newburger et al. 2003; Newburger and Bellinger 2006; Marino et al. 2012; Rollins and Newburger 2014).
Mechanical support/heart transplantation	• Patients receiving mechanical support both in the preoperative period or during postoperative care (either as extracorporeal membrane oxygenation or ventricular assist devices) are at risk of hemodynamic instability; besides, they are at increased risk of thromboembolic events; on the other hand, patients with heart transplantation are at increased risk for worse CNS outcome (Massaro et al. 2008; Marino et al. 2012; Rollins and Newburger 2014)

Classification of CNS Deficits

The risk of neurologic injuries and adverse neurodevelopmental outcomes are higher in neonates and infants with congenital heart disease (Sherlock et al. 2009; Adams-Chapman et al. 2018). In these patients, CNS deficits are categorized under three main classes:

- Neurologic deficits
- Neurocognitive and neurodevelopmental disorders
- White matter injuries (WMI), including periventricular leukomalacia (PVL)

Neurologic Deficits

Neurologic injuries are a common finding in neonates and infants with underlying congenital heart diseases. These lesions are among the most important perioperative complications in these patients. The following are among the most common neurologic disorders in these patients (Kinney et al. 2005; Chen et al. 2009; Sherlock et al. 2009; Block et al. 2010; Gaynor et al. 2015):

- White matter injuries (including periventricular leukomalacia or diffuse white matter gliosis)
- Stroke with a 10% prevalence; half occurring preoperatively (Chen et al. 2009)
- Seizures
- Intraventricular hemorrhage (IVH)
- Visual disturbances
- Gray matter lesions
- Focal neurologic injuries

Neonatal stroke and periventricular leukomalacia (PVL) are the two most significant lesions in patients undergoing congenital heart surgery (Sherlock et al. 2009). However, seizures, either convulsive or non-convulsive, are among the most serious neurologic complications after congenital heart surgery in neonates and infants; nonconvulsive seizure presenting only as electroencephalography (EEG) seizure activity is much more common than convulsive seizures in this patient population (Abend et al. 2013).

Neonatal Seizure

Neonatal seizures remain a great challenge and a clinical dilemma. Among the main reasons for this fact include the following:

- Ambiguous presentations
- Failure of immediate detection
- The paucity of evidence-based management protocols; especially regarding the standard treatment
- Poor outcomes
- Adverse neurodevelopmental outcome and epilepsy are the main considerations as the aftermath of neonatal seizure in the long term, mandating careful follow-up for neonatal seizure patients

The incidence of neonatal seizure is the highest among all age groups: 1.5–3 per 1000 live births (Silverstein and Jensen 2007; Jensen 2009).

Etiology

The following four classes constitute the main etiologies for neonatal seizure in 80–85% of patients (Silverstein and Jensen 2007; Jensen 2009; Kang and Kadam 2015):

- Hypoxic-ischemic encephalopathy (HIE)
- Hemorrhagic events
- Metabolic disorders
- Infectious processes

Among all of the above, HIE is the etiology of neonatal seizure in about two-thirds of patients (Jensen 2009). However, these different etiologies lead to different severities of the disease and diverse outcomes; some of the seizures with non-HIE etiologies have good outcomes; while the outcome in HIE is much worse. So, the underlying mechanism in neonatal seizures remains a crucial issue in the diagnosis and treatment of neonatal seizures (Kang and Kadam 2015).

Risk Factors

The risk factors for seizures in neonatal and pediatric patients undergoing cardiac surgery are diverse and heterogeneous. The main risk factors in this specific patient population include:

- DHCA
- Longer duration of circulatory arrest
- Asphyxia at birth
- Respiratory distress
- A complication due to the use of extracorporeal membrane oxygenation (ECMO)
- Some of the underlying cardiac anomalies like ventricular septal defect (VSD) (Helmers et al. 1997; Jensen 2009)

Diagnosis

In the diagnosis of neonatal seizure, the availability of both amplitude-integrated EEG (aEEG) and standard EEG is very decisive unless aEEG is utilized in neonatal intensive care unit (NICU), a considerable part of patients with neonatal seizure would be undetected (Boylan et al. 2015; Kang and Kadam 2015). aEEG is a bedside tool for neurophysiologic assessment and uses fewer channels than standard EEG; so, aEEG is much easier, both regarding its use and interpretation and could help earlier diagnosis much more than conventional EEG. However, standard EEG is more sensitive for the diagnosis of seizure, but aEEG does not need to be exclusively interpreted by a neurologist. Of course, standard EEG remains the decisive method of diagnosis for neurophysiologic assessments. A full discussion on CNS monitoring tools including EEG could be found in chapter "Perioperative Cardiovascular Monitoring in Congenital Heart Disease Patients"—"CNS monitoring." For long-term brain imaging and follow-up studies, magnetic resonance images (MRIs) are one of the best available options. Long-term outcome differs based on the underlying etiology; hence, long-term follow-up is a basic rule.

Treatment

Although a considerable number of studies have been done to determine the best therapeutic protocol for neonatal seizures, satisfactory evidence is still lacking. However, phenobarbital is considered as the drug of choice, but, its efficacy and the pharmacologic profile of the drug is still the subject of some studies. The final word in the selection of the best available anticonvulsant therapeutic protocol is to be said (Hellstrom-Westas et al. 2015; Kang and Kadam 2015).

Neurocognitive and Neurodevelopmental Disorders

Congenital heart disease increases the risk of neurodevelopmental performance including the scores on intelligence, alertness, executive functions, attention and memory, and possibly the daily life care and school function (Sterken et al. 2015). Since neurodevelopmental and neurocognitive aspects of care are of great concern, clinicians have tried to improve this aspect of postoperative outcome; however, difficulties in

daily functioning and academic achievements in such patients remain a problem (Gaynor et al. 2015).

Neurocognitive disorders are categorized under a common framework in DSM-5. Generally, the main characteristic of neurocognitive disorders is "*a decline from a previously attained level of cognitive function*" and includes "*delirium, mild cognitive impairment, and dementia*" (Hsia and Gruber 2006; Snookes et al. 2010; Sachdev et al. 2014; Simpson 2014; Pape et al. 2021). Based on DSM-5 classification, there are six neurocognitive domains:

1. Perceptual motor function: visual perception, visuoconstructional reasoning, perceptual-motor coordination
2. Language: object naming, word-finding, fluency, grammar and syntax, receptive language
3. Learning and memory: free recall, cued recall, recognition memory, semantic and autobiographical long-term memory, implicit learning
4. Social cognition: recognition of emotions, theory of mind, insight
5. Complex attention: sustained attention, divided attention, selective attention, processing speed
6. Executive function: planning, decision making, wording memory, responding to feedback, inhibition flexibility

For the assessment of cognitive function, both clinical neurodevelopmental testing and follow-up magnetic resonance imaging (MRI) are of great importance; these two assessment tools remain the main surrogate outcome measures in the aftermath of congenital heart surgeries (Kaltman et al. 2010). For example, there is a specific type of brain injury seen in pediatric patients undergoing congenital heart surgery described by Soul et al.; they found subtle hemorrhagic events, demonstrated in brain MRI as "***foci of hemosiderin***"; in their study, these lesions were found in postoperative brain MRI and they described them as small hemorrhagic lesions with the etiology being different from the etiology of hypoxic-ischemic lesions or periventricular leukomalacia. These subtle hemorrhagic foci could be detected by exact MRI studies during serial assessments; also, they hurt the neurodevelopmental outcome of the children undergoing congenital heart surgery (Soul et al. 2009; Albers et al. 2010).

White Matter Injuries (WMI) Including Periventricular Leukomalacia (PVL)

In recent years, the improved quality of care in neonatal intensive care unit (NICU) has led to improvements in outcome in some aspects of WMI. However, there are still areas that are not much well managed. For a better understanding, we will first review the current classification for WMI based on the many studies performed in this area, both on animal and human samples (Segovia et al. 2008; Buser et al. 2010; Back et al. 2012; Dean et al. 2013; Back 2014, 2015; Back and Miller 2014; McClendon et al. 2014; van Tilborg et al. 2016; Mehrotra 2019; Ismail and Semien 2021; Janjua et al. 2021).

White matter injury occurs in two forms:

- Selective death of premyelinating oligodendrocytes which is more common and involves widespread lesions which are often detected in autopsies and yield to microscopic cysts; however, they are not very well defined by MRI; this type of lesions leads to the widespread renewal of premyelinating oligodendrocytes; then leading to reactive gliosis and the outcome is arrest in the maturation of premyelinating oligodendrocytes.
- The other form is widespread "pan-cellular death and necrosis" resulting in cystic PVL and larger lesions compared with the first group; this type of lesion leads to glial and axonal loss.

Both of these lesions lead to "myelination failure" which is discussed more in the next paragraphs.

Periventricular Leukomalacia (PVL)

PVL necrosis in deep white matter which is presented as multifocal symmetrical necrosis areas is often known as cystic PVL or cPVL. The process of necrosis involves premyelinating oligodendrocytes; these necrotic areas are often adjacent to the external angles of the lateral ventricles (Rezaie and Dean 2002; Back 2014; McClendon et al. 2014; Zaghloul et al. 2017). The resulting clinical signs of neurologic damage typically usually start to present in early childhood; while the clinical outcomes in the long term would rely on the spread of the lesions and include a list of the clinical presentation discussed in the next paragraphs (Folkerth 2006; Zaghloul et al. 2017).

Risk Factors

These are among the most reported risk factors for PVL (Herzog et al. 2015; Shang et al. 2015):

- Prematurity
- Preterm infants
- Gestational age of ≤32 weeks
- Perinatal infections (especially chorioamnionitis)
- Perinatal hypoxia and/or respiratory distress
- Low-birth-weight infants
- Maternal obesity
- Preterm premature rupture of the membranes (PROM)

There also seems to be a negative correlation between gestational age and birth weight (Shang et al. 2015). Resch et al. in a cohort study found "respiratory distress syndrome, preterm premature rupture of the membranes, and chorioamnionitis" as the most common clinical findings associated with PVL (Resch et al. 2015). Chorioamnionitis has been proposed as a risk factor for PVL in many studies, mainly due to its inflammatory effects; however, some controversy exists (Wu and Colford 2000; Chau et al. 2014; Herzog et al. 2015).

Mechanism of Injury

Decreased perfusion of the periventricular areas during systemic hypotension and inflammatory responses during the perinatal period have been proposed as the two main mechanisms of injury for PVL. In infants with PVL, higher serum levels of interleukin-1 beta (IL-1β) and tumor necrosis factor-alpha (TNF-α) have been demonstrated, and these are accompanied by other pro-inflammatory mechanisms leading to white matter damage in PVL although antenatal steroids might suppress the prevalence of PVL (Canterino et al. 2001; du Plessis and Volpe 2002; Rezaie and Dean 2002; Kohelet et al. 2006; Tsukimori et al. 2007; Hagberg et al. 2015; van Tilborg et al. 2016). New insights into inflammatory mechanisms of PVL are emerging. Vontell et al. demonstrated increased expression of glial toll-like receptor 3 (TLR3) protein in infants with PVL which could result in impaired development in preterm infants (Vontell et al. 2013, 2015).

However, the most probable pathologic mechanism of PVL is that etiologic insults result in "acute death in premyelinating oligodendrocytes." This event occurs potentially by microglial activation and liberation of "reactive oxygen and nitrogen species." These oligodendrocytes should normally be changed to myelinating cells; finally, their failure in normal growth leads to a pathologic process associated with "rapid regeneration of premature oligodendrocytes" which happens during a crucial period of neural circuitry development. Immature neurons are more resistant to cellular death; however, even after the mildest insults in premature neurons, extensive interference and disruption are seen in the maturation process of their dendritic synapses and dendritic latticework; the final result of these insults is impaired cerebral growth and development in the neonatal brain and thereafter (Haynes et al. 2003; Back 2014, 2015; Back and Miller 2014; McClendon et al. 2014; van Tilborg et al. 2016).

Prevalence

In neonates with congenital heart disease, PVL is a frequent finding even before they undergo cardiac surgery (Miller et al. 2007) and more than 50% of these patients demonstrate mild ischemic CNS lesions in brain MRI during the postoperative period, often in the form of PVL (Mahle et al. 2002). Galli et al. found that more than 50% of neonates undergoing cardiac surgery had PVL after surgery, however, in their study, PVL occurred rarely after in older infants after cardiac surgery (Galli et al. 2004).

Clinical Presentation of PVL

PVL has been demonstrated as a risk factor for the following abnormalities with different frequencies (Gurses et al. 1999; Kohelet et al. 2006; Glass et al. 2008; van Haastert et al. 2008; Resch et al. 2015; Shang et al. 2015; van Tilborg et al. 2016). These include the following:

- Visual impairment
- Auditory disorders
- Sensory disorders
- Gross motor function
- Convulsive or non-convulsive seizure (not frequent comorbidity; maximum in 25% of PVL patients)
- Mental retardation
- Language impediments
- Cognitive impairment
- Psychological disturbances (like autism-spectrum disorders, ADHD, and other psychological disturbances)
- Abnormal gait patterns
- Intraventricular hemorrhage

Infants with PVL are at increased risk of seizure; also, it has been demonstrated that in infants with PVL, the following risk factors are significant independent predictors of seizures (Kohelet et al. 2006):

- Decreasing gestational age
- Intraventricular hemorrhage
- Post-hemorrhagic hydrocephalus
- Sepsis
- Necrotizing enterocolitis

Diagnosis

Besides the clinical findings, especially in long-term follow-up terms, the diagnosis was commonly confirmed using cerebral ultrasonography; however, recent studies have shown MR images of significantly greater diagnostic value which could detect lesions not detected by cerebral ultrasonography; neuroimaging methods and their biomarkers are not only used as diagnostic and prognostic markers but also, they are used as efficient tools for follow-up assessments, long-term outcome assessment and evaluation of neuroprotective measures (Panigrahy et al. 2012; Kwon et al. 2014; Englander et al. 2015; Van't Hooft et al. 2015).

Treatment

Currently, no well-defined treatment for PVL is available; however, the current research in the field of "molecular mechanisms underlying impeded oligodendrocyte maturation" may help us discover novel therapies; till then, recognition of at-risk patients, prevention of additional injuries, and rehabilitation for the aftermath of the disease remains the mainstay (van Tilborg et al. 2016).

Postoperative Delirium in Pediatric Patients

Postoperative delirium after pediatric cardiac surgery is a challenging issue. Based on DSM-V criteria, delirium is "characterized by disturbance in attention that makes it difficult for the individual to direct, sustain and shift their focus" (Joshi et al. 2012). According to Sachdev et al., these are the main diagnostic features of delirium based on DSM-V criteria (Sachdev et al. 2014; Patel et al. 2017; Staveski et al. 2021):

1. Disturbance in attention or awareness
2. Time course of the disturbance is short, hours to a few days, with fluctuation during the daily time course
3. Cognition disturbance like "memory deficit, disorientation, language, visuospatial ability, or perception"
4. Items #1 and #3 are not better explained in the context of any other neurocognitive disorder

5. Clinical and/or paraclinical findings demonstrate that the disturbance is directly due to physiological results of another underlying medical and/or substance-induced disorder

Due to a to paucity of evidence, recommended practice in this issue requires some extrapolation from adult cardiac surgery to pediatric cardiac surgery, and clinical practice is based on consensus than pure evidence; for example, it is recommended not to use benzodiazepines for the treatment of postoperative delirium after pediatric cardiac surgery just because studies in adult cardiac surgery has demonstrated these drugs as potentially deliriogenic.

Given the limitations, the consensus is in favor of pharmacological treatments for postoperative pediatric delirium in cases that non-pharmacological treatments are unsuccessful intending to prevent the child from potential self-hazards, discomforting or endangering himself/herself. If a child is delirious, he/she may potentially interfere with the treatment process; on the other hand, a well-treated child may allow the treatment team to open "appropriate environment" for the parents to take part in the process of care. Additionally, if a delirious child remains untreated, the risk of unplanned events decreases; events like unplanned endotracheal extubation or loss of intravenous lines, arterial line, or central line (Malarbi et al. 2011).

Clinical Assessment and Monitoring of Delirium in Pediatric Cardiac Surgery

It is necessary to perform repeated and specific methods for screening of delirium. This approach mandates validated delirium scoring systems developed for pediatric age groups (Daoud et al. 2014; Baron et al. 2015). These include:

- pCAM-ICU: the Pediatric Confusion Assessment Method for the Intensive Care Unit (for ages ≥5 years)
- PAED-Scale: the Pediatric Anesthesia Emergence Delirium Scale (for ages 1–17 years)
- CAP-D: the Cornell Assessment of Pediatric Delirium; which is a modification of the PAED designed for detection of hypoactive delirium
- CAP-DI: the revised Cornell Assessment of Pediatric Delirium

Treatment of Postoperative Delirium

Pediatric delirium when recognized responds well to therapy, including both pharmacologic and non-pharmacologic treatments. Once the pharmacologic treatment is tailored appropriately, it improves the course of delirium (Schieveld et al. 2007; Madden et al. 2011; Hipp and Ely 2012).

A detailed discussion on pharmacotherapy of postoperative delirium after pediatric cardiac surgery is presented in chapter "Cardiovascular Pharmacology in Pediatric Patients with Congenital Heart Disease"; Table 20 provides a list of drugs used for the treatment of pediatric ICU delirium. The principles of treatment in hyperactive delirium include the following key items:

- Some anesthetic drugs may prevent delirium when given as premedication or as an analgesic during anesthesia. These may include clonidine, propofol, ketamine, halothane, dexmedetomidine, gabapentin, midazolam, magnesium, hydroxyzine, dexamethasone, or opioids (e.g., fentanyl). These agents decrease the chance and/or severity of postoperative delirium in children undergoing general anesthesia.
- Pain management in combination with sedative medication especially with alpha-2 agonist activity has an important role in the prevention of postoperative pediatric delirium (Dahmani et al. 2010, 2014; Costi et al. 2014; Lambert et al. 2014; van Hoff et al. 2015).
- Some anesthetic agents make provoke delirium after general anesthesia. Among volatile agents, sevoflurane could increase the chance of delirium especially when the patient is not pre-medicated (Messieha 2013).
- Pharmacologic treatment, when started, should be continued until full treatment and

should be tapered off; abruptly discontinuation is not advised.

- Intravenous haloperidol and oral risperidone are the main drugs used for pharmacologic treatment of delirium. Risperidone has fewer adverse events than haloperidol. Unfortunately, risperidone has no intravenous form, and intravenous forms are at times the preferred choice while in the ICU. Atypical antipsychotics like quetiapine are used as off-label pharmacological agents for adult delirium. However, there are limited data for their application in pediatric delirium; the median daily dose of quetiapine is about 1.3 mg/kg/day with a median treatment duration of 12 days (Warshaw and Mechlin 2009; Madden et al. 2011; McPheeters et al. 2011; Joyce et al. 2015).
- Delirium scoring during pharmacologic treatment is critical and should be performed at least three times a day. At least one of the scoring systems named in the previous paragraphs should be used as a routine assessment tool. When any of these tools is chosen, monitoring the level of sedation/agitation, assessment of patient behavior regarding psychometric performance, and the clinical opinion of the caregivers should be among the main considerations (Schieveld et al. 2009; van Dijk et al. 2012; Daoud et al. 2014).
- The main complications of pharmacologic therapy include extrapyramidal symptoms (including dystonia, akathisia, and hyperpyrexia) and lengthening of QTc interval which might lead to lethal Torsade de Pointes (Brahmbhatt and Whitgob 2016).

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Perioperative Management of Endocrine Problems in Pediatric Cardiac Surgery Patients

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Abstract

Perioperative care of patients with endocrine disorders undergoing congenital heart surgery includes a wide range of different diseases. This chapter deals with perioperative management of patients receiving steroids, perioperative management of the dosage of glucocorticoids, perioperative management of the pituitary gland, perioperative management of diabetes mellitus patients, and perioperative management of patients with metabolic disorders. Each of the different types of disorders in this chapter has a significant role in the outcome of the patients with congenital heart disease; so a practical approach to each topic is discussed here.

Keywords

Congenital heart surgery · Perioperative care · Steroid · Pituitary gland · Diabetes mellitus · Metabolic disorders

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Perioperative Management of Patients Receiving Steroids

Acute physical or emotional stresses are the most important activators of the hypothalamic-pituitary-adrenal axis (HPA); surgery is one of the most potent activators of the axis. The degree of activeness depends on factors such as the type of surgery and the anesthetic agents used during the procedure (Joseph et al. 2016; Smithson et al. 2019; Aruna et al. 2021; Chaves et al. 2021).

The level of cortisol changes during both major and minor surgeries. It falls initially after premedication and rises rapidly during surgery. Its rising trend continues after surgery, i.e., dur-

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ing reversal of anesthesia, extubation, and recovery period, mainly in response to pain. The pattern of response is similar in minor surgeries but the peak values are smaller than in major surgeries. The peak values occur immediately (4–6 h) after surgery and fall to reach their baseline value after 24 h (Maeda et al. 2016; Teagarden and Mastropietro 2017; Tang et al. 2019).

When to Suspect an Impaired HPA Axis?

The exact period it takes for a patient to become adrenally suppressed while treated with glucocorticoids, and the time it takes to recover adrenal function after discontinuation of steroids, are not known; however, it depends on the dose, time of day, and the duration of the previous glucocorticoid therapy (Bhalla et al. 1999; Skippen et al. 2008; Kalaria et al. 2020).

Here, a list of patients is presented who should receive supplemental classified perioperative glucocorticoids; the dosage is recommended to be tailored according to the imposed load of the stress (Schroeder et al. 2003; Caprirolo et al. 2013; Wald et al. 2017; Li et al. 2020; Yasir et al. 2021):

- Patients receiving glucocorticoid with a dose similar to the physiologic range for 1–2 months.
- Patients receiving prednisone or its equivalent in doses higher than 20 mg daily for more than 3 weeks; in this group, one of the three regimens are suggested: methylprednisolone 16 mg/day, dexamethasone 2 mg/day, or hydrocortisone 80 mg/day.
- Clinical Cushing's syndrome patients receiving glucocorticoids.
- This group of patients is suggested to receive additional perioperative glucocorticoid coverage during the perioperative period per the magnitude of the stress.

Patients with Non-Suppressed HPA Axis

The following patients are categorized under this title (Caprirolo et al. 2013; Liu et al. 2013; Hill et al. 2020):

- Patients who have received any dose of glucocorticoid for less than 3 weeks.
- Patients who have received morning doses of prednisone with a dose of less than 5 mg daily or its equivalent including methylprednisolone (4 mg daily), dexamethasone (0.5 mg daily), or hydrocortisone (20 mg daily) for any duration of use.
- Patients who have received prednisone with a dose of less than 10 mg daily or its equivalent every other day.

Suggested treatment for this group of patients is to receive a maintenance dose of their normal daily dose of glucocorticoids during the perioperative period. In this group of patients, it is not necessary to evaluate the possibility of HPA axis suppression, because the test could not accurately predict the development of adrenal crisis postoperatively. It is recommended to monitor these patients for any evidence of hemodynamic instability perioperatively.

Patients with the Uncertain Status of the HPA Axis

In those patients currently taking doses of 5–20 mg of prednisone (or its equivalent) for more than 3 weeks, there is considerable variability in the HPA axis; the main reasons are:

- These patients are faced with a suppression that does not correlate well with age, sex, dose, or duration of therapy.
- There are differences in rates of glucocorticoid metabolism.
- However, doses lower than the equivalent of 5 mg of prednisone daily taken in the evening

may disrupt the normal diurnal variation and the way the patient responds to surgical stress.

There are two approaches for this group of patients: the first approach is the perioperative administration of glucocorticoids; however, the second one, which is recommended for those patients who have enough time, is to measure morning serum cortisol levels or evaluate the responsiveness of the adrenal function to adrenocorticotropic hormone (ACTH) stimulation before surgery (Caprirolo et al. 2013; McGauran et al. 2017; Wald et al. 2017; Fudulu et al. 2020b).

Other Groups of Patients Mandating More Sophisticated Care

For patients using inhaled steroids and topical glucocorticoids, the inhaled glucocorticoids might exert suppressive effects on the HPA axis with the following doses:

- An inhaled glucocorticoid with daily doses greater than 0.8 mg.
- Fluticasone with a daily dose of 750 μg (1500 μg daily for other inhaled glucocorticoids (IGCs)) for more than three weeks before surgery.
- Beclomethasone, triamcinolone, or budesonide with a daily dose of 1.5 mg.
- Before surgery, using ≥2 g/day of very high potency topical corticosteroids for more than 3 weeks; however, the potency or dose of topical steroids that could induce secondary adrenal suppression is not determined clearly. Some factors such as application to a large surface area of skin or highly permeable areas, use of high-potency glucocorticoid as little as 2 g/day for two or more weeks, long-term use, occlusive dressings, poor skin integrity, liver failure, and young age could increase the risk of adrenal suppression.
- Also, the HPA axis should be evaluated in Cushingoid patients or those with signs or symptoms of adrenal insufficiency (AI).
- Patients using intra-articular and spinal glucocorticoid injections; for patients who have received three or more intra-articular or spinal glucocorticoid injections during the last 3 months before surgery or those with a Cushingoid appearance, HPA axis evaluation is recommended.

How to Manage the Dosage of Glucocorticoids in the Perioperative Period

The required dose of glucocorticoids will be determined according to the three main factors, including the preoperative dose and the duration of glucocorticoid use as well as the anticipated duration of surgery (Graham et al. 2019).

Surgical Procedures

The evidence regarding the perioperative use of steroids in congenital adrenal hyperplasia is not conclusive yet; however, the following protocol is recommended for surgical procedures with duration of 30–45 min (Ahmed et al. 2019; Ng et al. 2020; Yau et al. 2021):

- 0–3 years: Hydrocortisone 25 mg intravenous (IV)
- 3–12 years: Hydrocortisone 50 mg IV
- 12 years and older: Hydrocortisone 100 mg IV

The initial bolus dose with mentioned dosage is followed at a constant rate over 24 h. Considering the clinical improvement of the patient, the stress doses of hydrocortisone are tapered rapidly by 50% reducing the dose, daily. Meanwhile, for surgeries with a duration longer than 30–45 min, the suggested protocol includes the following recommendations (Melin et al. 2020; Yau et al. 2021):

- Before induction of anesthesia: rapid intravenous injection of hydrocortisone with a dose of 25 mg/m^2.
- During surgery: an approximately 50 mg/m^2 dose of hydrocortisone as a constant intravenous infusion.

- For the first 24 h after surgery: an approximately 25–50 mg/m^2 dose of hydrocortisone as a constant intravenous infusion for patients unable to take oral hydrocortisone postoperatively.
- 24 h after surgery: hydrocortisone replacement therapy with the same dose is continued three to four times by constant IV infusion or orally. In cases, with significant hypotension or electrolyte abnormalities, additional hydrocortisone may be needed. The stress dosing is continued until the patient becomes stable hemodynamically and afebrile and can tolerate oral intake of glucocorticoids.
- For switching the intravenous administration to the oral form, the intravenous dose is reduced and triple-dose oral hydrocortisone replacement therapy with a dose of 30–50 mg/m^2 daily is initiated.
- The dose of oral hydrocortisone replacement therapy could be gradually reduced to reach its maintenance levels in 5 days.
- The maintenance dose for patients with primary and secondary adrenal insufficiency is 10–15 mg/m^2 and 6–8 mg/m^2 daily, respectively.
- For patients with mineralocorticoid deficiency, fludrocortisone at maintenance doses is initiated as soon as the patient can tolerate oral fluids.
- An alternative approach that is followed by some centers is the continuous infusion of hydrocortisone with a daily dose of 100 mg/m^2 after the initial bolus dose mentioned above.
- For minor procedures under local anesthesia and in most radiologic studies, no extra supplementation is needed.
- For moderately stressful procedures such as barium enema, endoscopy, or arteriography, give a single 100 mg/m^2 IV dose of hydrocortisone just before the procedure.

Perioperative Management of the Pituitary Gland

The pituitary gland as the "master gland" has an important role in the secretion of five groups of hormones; some of them directly regulate the secretion of other endocrine glands and some others have an important role in preventing water and electrolyte imbalance, while it could be highly affected by the perioperative events in cardiac surgery (McGauran et al. 2017; Yarigholi et al. 2018).

In the perioperative period, it is very important to diagnose any degree of deficient secretion of adrenocorticotropic hormone (ACTH), thyroid-stimulating hormone (TSH), and antidiuretic hormone (ADH) from either the anterior or posterior pituitary gland. It may cause central adrenal insufficiency (AI), central hypothyroidism, and central diabetes insipidus (DI). On the opposite, deficient secretion of Follicle-stimulating hormone (FSH), Luteinizing hormone (LH), prolactin, and growth hormone (GH) has less effect on the perioperative management of children, although GH has an important role in glucose hemostasis and in providing euglycemic state, especially in the neonatal period and early infancy (Wald et al. 2011).

Central Adrenal Insufficiency

Its signs and symptoms include fatigue, weakness, arthralgia, myalgia, and hypoglycemia. It does not include volume depletion, salt wasting, and hyperkalemia that occur because of mineralocorticoid deficiency, but dilutional hyponatremia is not uncommon in this situation because cortisol deficiency—even without aldosterone deficiency—may cause free water retention. The diagnosis of central adrenal insufficiency is the same as the primary form of this life-threatening situation and also, is very important in the perioperative management of children, the same as adult patients. It must be tested by measuring serum cortisol levels at 8:00 a.m. The values below 3 μg/dL are suggestive of cortisol deficiency and values above 18 μg/dL are indicative of cortisol and ACTH sufficiency. For cortisol values persistently between these two numbers (3 and 18 μg/dL), it is recommended to have an ACTH reserve test, which is discussed in more detail in other parts of this chapter. It is very important to know that partial ACTH deficiency may be with few or no significant signs or symp-

toms and so, in all patients with suspected pituitary insufficiency, the adequacy of the hypothalamic-pituitary-adrenal axis should be evaluated biochemically. The appropriate treatment of central AI, the same as the primary form, is very important and lifesaving in the perioperative management of children. It will be discussed in different parts of this chapter (McGauran et al. 2017; Fudulu et al. 2020a, b).

Central Hypothyroidism

Central hypothyroidism is defined by low or below normal free T4 with normal or minimally increased TSH values. It may have different degrees of weight gain, fatigue, constipation, cold intolerance, dry skin, and bradycardia. When the diagnosis is established by the laboratory, it is recommended to start levothyroxine before anesthesia and surgery to minimize perioperative problems such as delayed recovery from anesthesia, neuropsychiatric disturbances, and ileus and electrolyte abnormalities.

The initial dose is the same as in primary hypothyroidism, but, in dose adjustment, it is important to know that TSH values were normal from the first time and through the course of treatment; so, we must consider free T4 values to adjust the levothyroxine dosage.

The second important point in this area is that glucocorticoid replacement therapy is essential before levothyroxine if there is a concomitant adrenal insufficiency as a part of hypopituitarism. It is because of the effect of thyroid hormones that increases cortisol metabolism and consequently precipitates the adrenal crisis.

Central Diabetes Insipidus (DI)

Childhood central DI, due to deficient secretion of ADH, is caused by familial or congenital disorders, head trauma, neurosurgery, Cantrell nervous system tumors in the hypothalamus or pituitary region especially craniopharyngiomas, infiltrative disorders, hypoxic encephalopathy, and anorexia nervosa. But the most common causes are cranial tumors, Langerhans cell histiocytosis, and idiopathic conditions. The diagnosis is mainly made based on the presence of polyuria (urine output exceeding 2 L/m^2/day) and polydipsia with elevated or high normal serum sodium concentration and urine specific gravity less than 1.005 (Hui et al. 2021; Nakatani et al. 2021; Priya et al. 2021).

In children with central DI, before inducing anesthesia, it is important to be sure about being patient in the euvolemic and normo-natremic state. When the thirst mechanism is intact, in completely conscious adult patients, replacement of the water loss usually is done by oral intake. But in young children and in those who are unable to drink fluids by themselves, the same as in unconscious patients, hypernatremia may occur. On the other hand, overtreatment of the pediatric patient with central DI may cause a more dangerous risk of water intoxication. So, the management of these children in the perioperative period is frequently complicated by the risk of hyper or hyponatremia and over- or underhydration (Mutter et al. 2021; Robertson 2021).

Some physicians prefer not to replace ADH while elevating the total fluid intake of these children to about twice the maintenance amount, which is 3 L/m^2/day, to minimize the risk of hyponatremic encephalopathy and water intoxication; however, others prefer to manage DI children in the perioperative period with intermittent intramuscular vasopressin injection instead of using long-acting intranasal 1-desamino-8-d-arginine vasopressin (dDAVP) (Liu et al. 2019; Ji et al. 2020; Duicu et al. 2021).

Another group suggests treating these patients in perioperative management by using continuous low-dose IV infusion of aqueous vasopressin with fluid restriction. The infusion rate should be started with minimal dosage and titrated upward to the desired effect, which is urine output of less than 2 mL/kg/h. However, frequent monitoring of serum sodium concentration, urine volume, and urine-specific gravity is the most important part of all of these protocols. And finally, for any suspected patient to have pituitary insufficiency, the adequacy of the different pituitary axis should be tested before surgery to rule out life-threatening ACTH deficiency or other important involve-

ments such as central DI or central hypothyroidism (Liu et al. 2019; Duicu et al. 2021; Priya et al. 2021; Robertson 2021).

Perioperative Management of the Diabetes Mellitus Patients

Diabetes mellitus (DM) is a metabolic syndrome characterized by either a deficient secretion of insulin, impaired action of insulin, or both of these states; the resulting metabolic consequences are a major aspect of the disease. Clinically, it is manifested with inconsistent fasting or postprandial hyperglycemia, which includes agitated metabolism of protein and fat.

The results obtained from research studies related to diabetes mellitus considerably owe to two things to a very significant extent: the results of insulin secretion failure and the results of insulin interactions and functions in the target tissues and organs.

The prototypical laboratory findings in diabetes mellitus include:

- Fasting serum glucose of more than 126 mg/dL (i.e., 7 mmol/L).
- Loss of extra levels of glucose and ketone in the urine.
- Increased level of serum glucose to more than 200 mg/dL during the oral glucose tolerance test (the latter value in this test is an arbitrary one).

During the perioperative period, when caring the pediatric patients with diabetes mellitus undergoing cardiac surgeries, sophisticated care should be based on the following:

- The underlying pathophysiology of the disease.
- Perioperative metabolic management of the disease, including blood sugar level and the related biomarkers, including step-by-step management starting from the preoperative step to the operation theatre and leading to postoperative care.
- Institutional protocols for metabolic states, including perioperative fasting, postoperative nutritional support, insulin administration, hypoglycemia, and hyperglycemia should be followed.
- Electrolyte and trace elements are among the basic elements of care.
- The teamwork approach should be the cornerstone of the care.

Perioperative Management of Patients with Metabolic Disorders

Inborn errors of metabolism are a group of genetic disorders that result from the deficiency of an enzyme or its cofactor. The presence of these disorders could influence and complicate the management of surgery (Agana, Frueh et al. 2018). Clinical manifestations have a wide variety, from clinically asymptomatic to severe presentation.

Hypoglycemia

One of the most important issues that should be noticed in patients suffering from metabolic disorders is an increase in the risk of hypoglycemia during stressful conditions. So, regular fasting before surgery in these patients should be adjusted based on the patient's history and fasting tolerance. In short or minor procedures, surgery could be performed at noon or later after receiving glucose. In most situations, patients should receive fluid containing 10% glucose at a rate of 2500 mL/m^2/day and if needed, the rate of infusion must be changed to achieve a fixed blood glucose level.

Maintaining blood glucose level at >4 mmol/L (70 mg/dL) has been recommended (Hulkower, Pollack et al. 2014).

Phenylketonuria

Phenylketonuria (PKU) is a disorder of amino acid metabolism in which phenylalanine accumulates as a consequence of phenylalanine hydroxylase deficiency. Some of the presenta-

tions of PKU having an impact on the management of anesthesia are mental retardation, seizure, and friable skin. Those suffering from this disorder are susceptible to pressure damage due to their friable skin. Associated vitamin B_{12} deficiency may be seen in patients on strict diets (Agana, Frueh et al. 2018).

Preoperative Management

Adequacy of dietary therapy should be evaluated before the surgery by checking levels of phenylalanine and vitamin B_{12} within 72 h of elective procedures. Patients with a high plasma level of phenylalanine are at risk of seizures and abnormal neurological and/or emotional behaviors. Low phenylalanine level is associated with liver dysfunction, hypoglycemia, and abnormal neurological and psychological activity. In the case of abnormal levels, the elective operation may be postponed (Pode-Shakked, Shemer-Meiri et al. 2013). In patients with vitamin B_{12} deficiency, nitrous oxide can cause myeloneuropathy and increase B_{12} deficiency and hence should be avoided (Pode-Shakked, Shemer-Meiri et al. 2013; Agana, Frueh et al. 2018). It has been mentioned that more sensitivity of PKU patients to narcotics and respiratory depression following narcotic drugs might be a trigger for seizures during the post-anesthetic period (Pode-Shakked, Shemer-Meiri et al. 2013; Agana, Frueh et al. 2018).

Due to the susceptibility of the skin to eczema and its sensitivity, intubation and intravenous access should be done with caution. In case of emergency and major procedures, intravenous serum including dextrose could be used before and after the process (Yeoh et al. 2019).

Propionic and Methylmalonic Acidemia

Methylmalonic and propionic acidemia are autosomal recessive disorders, due to methyl malonyl-CoA mutase and propionyl-CoA carboxylase deficiency, respectively. Increasing protein catabolism during the perioperative period could raise the probability of acidosis. Information about the management of these patients during surgery is limited but there are some recommendations to minimize catabolism.

Preoperative Management

In emergency operations and major procedures (>30 min), plasma ammonia, pH, and blood gases should be checked. If serum ammonia is above 100 μmol/L or PH <7.3 or base deficit >10 mmol/L or when the patient's condition is not well, specialist consultation should be arranged and elective surgery should be canceled. Also, 48 h before elective surgery makes sure that the child is well; otherwise postpone the operation. The last metabolic investigation must have taken place less than 3 months before elective surgery (Baumgartner 2014). It has been suggested that elective surgery should be delayed four weeks after a recent infection. Stop feeds based on the minimal requirement for surgery and start carbohydrate-containing fluids or 10% glucose parenterally with appropriate electrolytes.

In vitamin B_{12} responsive patients, administer hydroxocobalamin in a dose of 1 mg parenterally, 1 day before and on the day of surgery. L-carnitine is another essential drug that should be given to these patients in the amount of 100 mg/kg/day (maximum 12 g for adults). The mentioned management should be maintained during the procedure. Intravenous lipid infusion (1–2 g/kg/day) is also helpful in longer operations. However, in patients with organic acidemia, Ringer's lactate solution should be avoided (Yeoh et al. 2019).

Nitrous oxide in methylmalonic acidemia may be avoided because it could exacerbate methylmalonic acidemia following the inhibition of cobalamin coenzymes. It is believed that some muscle relaxants including atracurium, cisatracurium, succinylcholine, and mivacurium should be avoided in propionic acidemia because their metabolites contain odd chain organic molecules. Because a small portion of fat in propofol is metabolized to propionic acid, this medication is not safe in propionic acidemia. Sensitivity to central nervous system depressant effects of volatile anesthetics and narcotics has been observed in hypotonic and lethargic patients with propionic acidemia. Another important complication in propionic acidemia is airway problems; these

complications could be minimized by delaying tracheal extubation. Until muscle strength is regained, analgesics derived from propionic acids such as naproxen and ibuprofen are not safe in patients with propionic acidemia and methylmalonic acidemia.

Postoperative Management

Start feeding when the patient is metabolically stable; after tolerating food, discontinue IV infusion. In the case of delayed or complicated recovery, ammonia, blood gases, and electrolytes should be evaluated. Antiemetic drugs including ondansetron could help patients but metoclopramide should be avoided. L-carnitine and glucose infusion should be continued. Adding intralipid is helpful in some cases (1–2 g/kg/day). After regaining full recovery and normal metabolic state, discharge is recommended (Baumgartner 2014).

Maple Syrup Urine Disease

Maple syrup urine disease (MSUD) is a disorder of branched-chain amino acids that results from defective carboxylation of these amino acids. Surgery and anesthesia introduce several problems in these patients. MSUD patients are at risk of hypoglycemia, cerebral edema, ketoacidosis, and neurological decline during the perioperative period (Agana, Frueh et al. 2018).

Preoperative Management

The following preoperative considerations are among the most important ones in these patients (Hulkower, Pollack et al. 2014):

- Blood ammonia, PH, electrolyte, and plasma amino acid concentration, as well as urine ketone, should be checked before the operation.
- Poor feeding could increase leucine concentration in plasma, so correction of dehydration before surgery is important.
- Administration of glucose is a good way to reduce catabolism.
- One of the lethal factors in these patients is overhydration, therefore conservative fluid management should be used to reduce the risk of brain edema.
- For selecting an anesthetic technique, it should be kept in mind that these patients are susceptible to convulsing; the administration of ketamine in MSUD patients with seizures is controversial.

Urea Cycle Defects

The urea cycle is a pathway that detoxifies ammonia to urea. The involvement of the enzymes in this pathway is called urea cycle disorder. The preoperative approach to urea cycle defects is similar to organic acidemia but in these patients, hyperammonemia should be avoided and monitored carefully; however, patients should have normal amino acids and ammonia before the procedure (Häberle et al. 2012, 2019; Summar and Mew 2018).

Perioperative Management

Intravenous arginine is indicated for patients receiving citrulline or arginine medication. The previous usual dose should be used, adding 2.5 g of arginine to 50 mL of 10% glucose administrated via syringe pump. Use the IV mixture of benzoate–phenylacetate for patients receiving either of these drugs and dilute the same way described for arginine. These drugs could be started in the postoperative period in the case of short procedures but it is recommended to administer intraoperatively in long operations, hyperammonemia states, and if there is a high probability of catabolism (Summar and Mew 2018; Häberle et al. 2019).

Fatty Acid Oxidation Defects

Acute breakdown of muscle following anesthesia is a problem in a patient with fatty acid oxidation disorder, especially in carnitine palmitoyltransferase II deficiency and long-chain hydroxyacyl-CoA dehydrogenase deficiency. Renal failure

may be seen in these patients due to myoglobinuria. Avoidance of fasting, and administrating intravenous glucose and water are the best strategies to prevent the complication of surgery and anesthesia. Start 10% glucose or higher if myoglobinuria is present. In some situations, insulin should be considered to maintain euglycemia catabolism (Hoffmann et al. 2017; Katz et al. 2017; Merritt et al. 2018; Yuasa et al. 2020).

Homocystinuria

Homocystinuria is a rare metabolic disease due to a defect of transsulfuration of precursors of cysteine. High plasma homocysteine has atherogenic and thrombophilic activity. Employing pyridoxine or betaine in the perioperative period decreases the risk of thromboembolism by lowering homocysteine concentration. Appropriate preoperative hydration and dextran infusion are suggested to prevent vein thrombosis (Slote et al. 2018; Valayannopoulos et al. 2019; Yeoh et al. 2019).

Mucopolysaccharidosis

Mucopolysaccharidosis (MPS) is a group of metabolic disorders in which glycosaminoglycan is stored in tissues and they are classified into seven types (I, II, III, IV, VI, VII, and IX) (Coutinho et al. 2012; Fecarotta et al. 2020). These disorders have some characteristics influencing anesthesia management including instability of the atlantoaxial joint, kyphoscoliosis, probability of cardiopulmonary involvement, and cord compression. Because of the difficulty of anesthesia in these patients, general anesthesia should be performed only in centers familiar with these diseases and by an experienced team; cervical instability has a high risk of anesthesia that is more prominent in Morquio (MPS IV), but also seen in MPS I and VI (Frawley et al. 2012; Dohrmann et al. 2020; Kubaski et al. 2020; Seker Yilmaz et al. 2021).

Preoperative Management

A careful history of anesthesia problems should be taken and a complete physical examination should be done. It is necessary to be aware of cardiopulmonary and cervical spine conditions. Determine blood pressure, Electrocardiography (EKG), and echocardiogram for all patients; evaluate pulmonary function test in case of kyphoscoliosis and reevaluate recent X-ray of the chest. If the patient is suspected of cord compression, magnetic resonance imaging (MRI) of the spine should be performed. Airway management and intubation are other major problems in MPS patients. They may be required smaller tubes than predicted for age. Macroglossia, micrognathia, and neck instability exacerbate these problems (Frawley et al. 2012; Moretto et al. 2018; Kubaski et al. 2020; Sawamoto et al. 2020; Zhou et al. 2020).

Postoperative Management

Postoperative airway obstruction may be seen in these patients, so postoperative care is also important. To reduce this problem, intraoperative corticosteroids may be needed before extubation. Waiting until the complete reversal effect of myorelaxants is recommended; another helpful way is the assignment of a nasopharyngeal airway. Hematologic consultation before elective surgery is recommended. Prescribing nitrous oxide as an anesthetic drug for these patients is discouraged (Frawley et al. 2012; Moretto et al. 2018; Yeoh et al. 2019).

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Regional Anesthesia and Perioperative Acute Pain Management in Pediatric and Adult Congenital Heart Surgical Patients

Casey Hamilton and A. Sassan Sabouri

Abstract

Effective acute perioperative pain management for cardiac surgery in both adults and children is essential to improve the patient experience and comfort and prevent the negative physiological consequences of poorly controlled pain in the postoperative period. There are a variety of sources of pain after cardiac surgery which may be influenced by patient factors, surgical approach, and lines or drains left in place. Poorly controlled pain may have negative impacts on patients, with increased discomfort and psychological stress, affect hemodynamics and the surgical stress response, and immune function. Formulating an individualized, multimodal approach with patient education and expectation management, systemic analgesics, and regional anesthesia approaches where appropriate, can provide effective analgesia and improve patient comfort. The field of acute pain management has significantly shifted over the past 10–20 years, with increased focused on maximizing multimodal non-opioid analgesics, which has coincided with advances in ultrasound-guided regional anesthesia techniques, including fascial plane blocks, which offer attractive options for adult and pediatric cardiac surgery patients. In this chapter we aim to summarize sources and assessment of pain after cardiac surgery, the evidence behind the systemic analgesics and regional anesthesia options that are being used, and avenues for further advances in the field.

Keywords

Acute pain management · Multimodal analgesia · Neuraxial anesthesia · Regional anesthesia · Cardiac surgery

Introduction

Cardiac surgery causes significant acute pain in both adults and children, resulting in negative physiologic and psychological consequences and could potentially worsen patient experiences and postoperative outcomes, including persistent postoperative pain (Rabbitts et al. 2015a). Persistent and chronic disabling pain is the leading factor of limiting

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activity and long-term disability (Rabbitts et al. 2015b). Acute pain is an unpleasant multifactorial experience with physiological components of actual or threatened tissue damage as well as psychological and emotional components (Shah and Siu 2019; Playfor et al. 2006). Adequate analgesia, especially after cardiac surgery, is essential to maintain stable hemodynamics, prevent increased and mismatched myocardial oxygen demand and supply, and may have positive impacts on other outcomes including cardiac arrhythmias, shorter time for mechanical ventilation, immune function, length-of-stay (LOS), and patient satisfaction (Chaney 2018). The proper assessment of, identification of types and sources, and treatment of perioperative pain in cardiac surgery patients is crucial to minimize the negative consequences of poorly controlled postoperative pain. The focus of analgesic strategies is shifting toward a multimodal approach, incorporating multiple non-opioid pharmacological therapies and regional anesthetic/analgesic techniques to target multiple pain sources and pathways and reduce the risk of any one class of therapies (Chou et al. 2016). Over the past 5–10 years, with increased utilization of ultrasound-guidance, there has been a significant expansion in regional anesthetics in a wide range of surgeries, including cardiac surgery in adults and children. This chapter will focus on the current evidence for multimodal analgesia after cardiac surgery and provide a preview of where the field may head in the future.

Innervation of the Thorax

Understanding the innervation of the thorax is essential when planning the optimal analgesic approach for each type of cardiac surgery, both for anticipating pain location, intensity, and the type, and for planning the most appropriate pharmacological and regional anesthetic choice to target pain appropriately. Much of the sensory innervation of the chest wall is provided by the thoracic intercostal nerves (Fig. 1). Thoracic spinal nerves exit their respective intervertebral foramen and then divide into dorsal rami, which innervate the posterior muscles, bones, joints, and skin, and ventral rami that become the intercostal nerves and supply innervation to the lateral and anterior chest walls. The intercostal nerve courses with intercostal blood vessels between the internal and innermost intercostal muscles and gives off two major branches along its course: the lateral cutaneous branch at the midaxillary line traverses the internal and external intercostal muscles and the serratus anterior muscle, innervating the lateral chest wall, and the anterior cutaneous branch which traverses the internal and external intercostal membranes and the pectoralis major, ending in an accessory anterior cutaneous nerve, innervating the anterior chest wall and sternum. Sympathetic fibers from the upper thoracic levels and the cervical sympathetic chain can also be involved in visceral pain related to cardiac ischemia. In addition to thoracic spinal nerves, nerves from the brachial plexus are also pertinent to thoracic innervation related to cardiac surgery and regional anesthesia: the long thoracic nerve (C5–7), which courses over and innervates the serratus anterior muscle, thoracodorsal nerve (C6–8), which courses deep to and innervates the latissimus dorsi muscle, and the lateral pectoral nerve (C5–7) and medial pectoral nerve (C8-T1), which innervate the pectoral muscles. Finally, the vagus nerve (C3–5) is involved with visceral pain and referred shoulder pain from diaphragmatic and pleural irritation (Kelava et al. 2020).

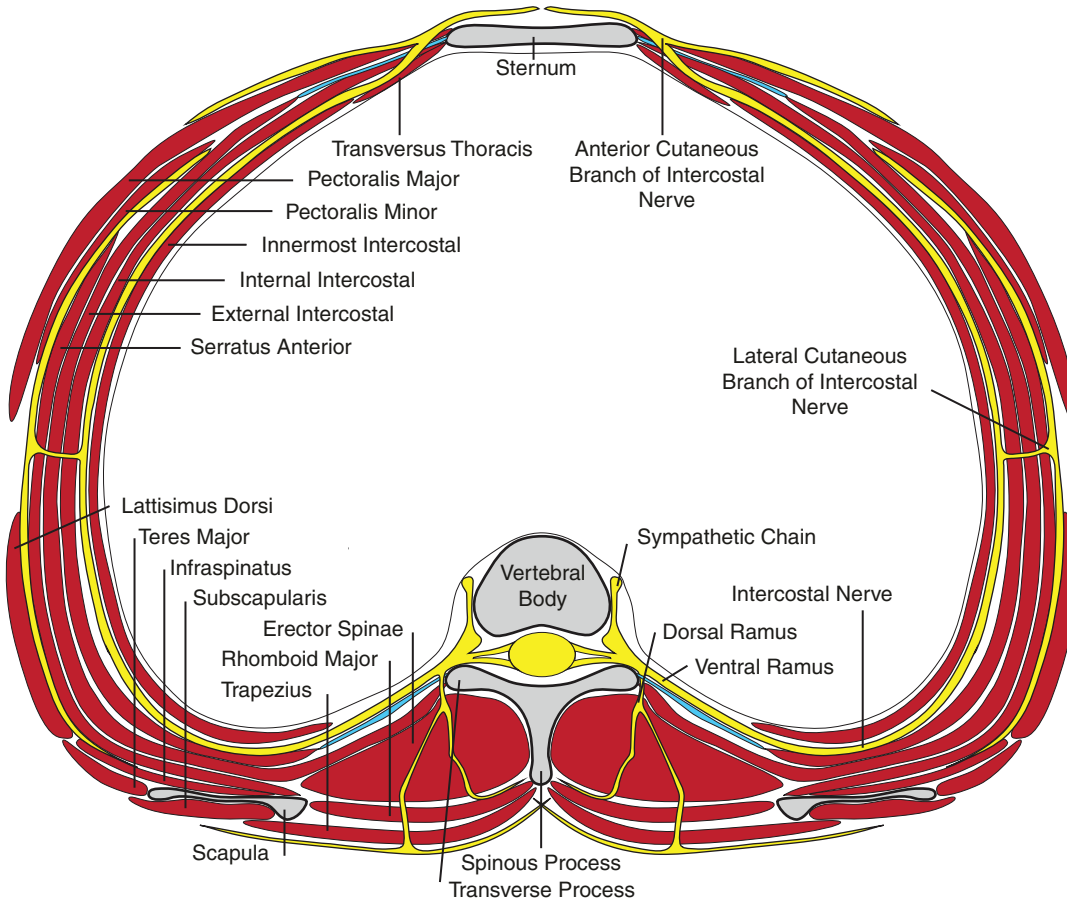

Fig. 1 Innervation of the thorax and chest wall. Chest wall muscles (red), bones (gray), and nerves (yellow) are depicted in an axial cross-section at the level of T5

Mechanisms of Pain After Cardiac Surgery

Cardiac surgery encompasses a wide range of procedures involving invasive approaches with extensive disruption of multiple tissue types. Acute postoperative pain is multifactorial with somatic nociceptive, inflammatory, visceral, and neuropathic components, which can also be exacerbated by the inflammatory stress response from cardiopulmonary bypass (CPB) (Cogan 2010; Jayakumar et al. 2019). The most common sources of pain include incisional pain at the skin and underlying tissues, sternotomy, thoracotomy, retraction of the sternum and ribs with possible rib fractures and dislocation of costochondral and costovertebral joints, nerve injury related to retraction, dissection, or surgical positioning, musculoskeletal pain from positioning and prolonged surgery, dissection of the vasculature including potential graft sites in the thorax as well as upper and lower extremities, and pain related to pleural and mediastinal drains (Chaney 2018; Cogan 2010). Thoracotomy and video-assisted or robotic-assisted minimally invasive surgeries with mini-thoracotomies can also result in intercostal muscle disruption with pressure and retraction on the intercostal neurovascular bundle can also cause significant nociceptive inflammatory and neuropathic acute pain. Neuropathic contributors to pain can be caused by damage to neurovascular bundles from rib retraction or dissection of the vasculature, including the internal mammary artery given its prox-

imity to anterior cutaneous branches of the intercostal nerves (Cogan 2010). Referred shoulder pain related to pleural/diaphragmatic irritation and pleural or mediastinal drains left in place postoperatively can also be a significant source of pain and discomfort for patients and often has a pleuritic component that can further worsen splinting and respiratory function. This referred pain can be present in up to 85% of patients after intrathoracic surgery (Mac et al. 2005).

Pain after cardiac surgery is usually the most severe on the first postoperative day, decreasing by the third day, with predominantly chest wall and incisional pain at first, and a shift to primarily musculoskeletal and osteoarticular pain later in the first postoperative week (Chaney 2006; Mueller et al. 2000). Pain related to any lower extremity vascular harvest sites may worsen after the first few days as the patient becomes more mobile. Also significant to consider is that tissue injury and inflammatory mediator release can lead to peripheral sensitization, where the threshold for pain signaling in the primary afferent nerve terminal is lowered. Central sensitization is related to a lower threshold for pain signal activation in the central nervous system, which can lead to primary hyperalgesia (increased response to a painful stimulus at the site of injury), secondary hyperalgesia (increased pain signaling from tissues surrounding the injury), and allodynia (a painful response to ordinarily non-noxious stimuli) (Zubrzycki et al. 2018). The appropriate identification of types and sources of pain is essential in formulating an effective analgesic plan to treat specific types and sources of pain, which may be different for each patient, surgery, and time-point in the perioperative course.

Consequences of Pain and Importance of Effective Analgesia After Cardiac Surgery

Poorly controlled pain after cardiac surgery can lead to negative hemodynamic, pulmonary, metabolic, immunologic, hemostatic, and psychological consequences (Cogan 2010; Jayakumar et al. 2019; Chaney 2006; Zubrzycki et al. 2018; Noss et al. 2018). Pain leads to sympathetic nervous system activation and results in tachycardia, vasoconstriction, and hypertension, which increase myocardial work and oxygen demand, and in a vulnerable heart in the postoperative period, can lead to adverse events including ischemia and arrhythmia in adults and children (Zubrzycki et al. 2018; Ramamoorthy et al. 2010). Avoiding factors that may cause such extremes, including pain and stress, may decrease the risk of ischemia from mismatched oxygen supply and demand (Ramamoorthy et al. 2010). Intrathoracic surgeries negatively affect respiratory function with a resultant restrictive respiratory pattern related to changes in respiratory mechanics, including decreased compliance, decreased functional residual capacity, and increased atelectasis. Poorly controlled pain and splinting amplifies these negative effects causing decreased tidal volumes, worsened atelectasis, and impaired cough effort and secretion clearance, all of which increase the risk for postoperative pulmonary complications, including infection, hypoxemia, increased work of breathing, and the need for prolonged mechanical ventilatory support (Zubrzycki et al. 2018; Sabanathan et al. 1990; Ballantyne et al. 1998). The perioperative stress response can also contribute to increased catabolism, hyperglycemia, impaired immune response, altered platelet function, which can be compounded by the concomitant stress response related to cardiopulmonary bypass (CPB). Increased catecholamines, cortisol, and insulin levels related to this surgical stress and inflammatory response may have negative effects on both adults and children, with worsened outcomes including increased risk of morbidity and more extended intensive care unit (ICU) length-of-stay (LOS) (Jayakumar et al. 2019; Noss et al. 2018; Humphreys et al. 2005). In addition to the negative physiological consequences of stress, which are exacerbated by inadequate perioperative pain control, both pediatric and adult patients can suffer increased anxiety, depression, sleep disturbances, and fatigue with potential for long-term psychological effects, including chronic pain and depression (Jayakumar et al. 2019; Zubrzycki et al. 2018). Specifically,

in pediatric patients, painful experiences early in life may confer increased risks of structural expansion of dorsal horn afferent nerves and increased pain sensitivity (Saini et al. 2020). Given the significant adverse impacts that poorly controlled pain may have after cardiac surgery, analgesia is an easily modifiable factor that can significantly improve patient experiences and outcomes and should be a major focus of the perioperative care of pediatric and adult congenital heart patients (Monahan et al. 2019; Nachiyunde and Lam 2018).

Risk Factors for Postoperative Pain

Appropriate planning with preoperative optimization of modifiable risk factors and patient education on expectations and coping strategies is vital to optimizing perioperative analgesia. Risk factors for acute pain after cardiac surgery include younger age, longer duration of surgery, and intrathoracic procedures (Cogan 2010). On the other hand, risk factors for persistent postoperative pain include young age, persistent nonanginal pain prior to surgery, baseline anxiety, moderate to severe pain on postoperative day three, and pain interfering with activities of daily living 1 week postoperatively (Choinière et al. 2014). Poorly controlled acute pain is a known risk factor for the development of chronic pain, with up to 40% of patients who undergo cardiac surgery experiencing chronic pain at 3 months and 16.5% at 1 year, with an estimated 11% of pediatric patients having chronic pain after cardiac surgery (Saini et al. 2020). Risk factors for the development of chronic pain, which are modifiable and could potentially improve outcomes by optimizing, include preoperative anxiety and the severity of acute pain in the first postoperative week (Cogan 2010; Choinière et al. 2014). Therefore, identifying patients vulnerable for both severe postoperative pain and at risk for persistent postoperative pain is crucial, and optimizing, including evaluating a patient's attitudes and beliefs and educating expectations and treatments for pain, is essential (Cogan 2010; Bigeleisen and Goehner 2015). Chronic pain after cardiac surgery is discussed separately in chapter "Chronic Postoperative Pain in Congenital Heart Disease Patients".

Assessing Pain After Cardiac Surgery

The proper assessment of pain, notably its type, location, source, severity, evolution over time, response to treatment, is essential in providing adequate analgesia to pediatric and adult patients after cardiac surgery. However, accurate assessment is often challenging, with barriers including patient factors with different beliefs, expectations, and pain experiences, factors that limit the ability of patients to effectively communicate their pain, including the need for sedation and mechanical ventilation, and communication barriers related to patient age and development, and postoperative delirium, all of which place patients at risk for inaccurate pain assessments and inadequate analgesia (Bigeleisen and Goehner 2015). Assessment of pain includes both subjective patient experiences including location, description, timing, duration, exacerbating or relieving factors, severity at rest and with movement, coughing, or deep inspiration, as well as physiological and physical exam findings including vital signs, tenderness, or pain with certain activities. Proper assessments should also include investigating for any adverse effects secondary to pain, including sleep and mood disturbances or limitations of functional status, as well as adverse effects from analgesics such as nausea and vomiting, dizziness, sedation or drowsiness, pruritis, constipation, dry mouth, headache, urinary retention, fatigue, confusion, nightmares, or hallucinations (Cogan 2010). There are numerous tools to aid in assessing pain in pediatric and adult patients, summarized below.

Assessing Pain in Adults

Multiple standardized assessments exist for assessing pain severity in patients, including simple, easy, and quick to complete scales such as

the Visual Analog Scale (VAS), Numeric Rating Scale (NRS), Verbal Rating Scale (VRS), and face pain rating scale. There are also more extensive assessments, such as the McGill Pain Questionnaire, which includes questions regarding the effect of pain on essential factors such as functional status, physical activity, well-being, and patient quality of life (Zubrzycki et al. 2018). As noted above, when using standardized scales, it is crucial to consider the entire clinical picture rather than the number or value in isolation, as factors including static and dynamic pain scores, effect on functional status and activates, and trends over time are more critical than single isolated values without a broader context on an individual's clinical status and trajectory.

Assessing Pain in Children

Pain assessments in children may be more challenging. They may be performed in more diverse ways than in adults, as pediatric patients span a wide range of ages, developmental stages, and communicative abilities. As pediatric pain assessment may be inherently more challenging and certain analgesics such as opioids have undesirable adverse effects, the risk for inadequate analgesia may be higher in pediatric patients with limited ability to articulate their experience. Other barriers to accurate assessments include low prioritization among medical staff and failure to assess regularly and repeatedly after analgesic therapy (Pollak et al. 2019). As detailed above, inadequate analgesia may confer risks of numerous poor outcomes. Specifically, children can have significant deleterious impacts on pain perception development, coping strategies, medical care experience, and chronic pain risk (Boric et al. 2017). As pediatric patients with congenital heart disease often have frequent and recurrent experiences with medical care, including potentially painful procedures, careful assessment, and adequate analgesia during the initial and each subsequent encounter are vitally important. There are several standardized pain assessments for children of different ages (Table 1) (Shah and Siu 2019; Diaz 2006). When possible, children should be familiarized with the planned assessment tool preoperatively. Assessment tools for infants, preverbal, and developmentally delayed patients have common features, including assessments of facial expression, crying, motor activities/responses, and vital signs.

Table 1 Standardized pain assessment tools for pediatric patients. Various standardized pediatric pain assessment tools including names/acronyms, intended age range for use, and components included in the assessment

Assessment	Age	Components
CRIES	Premature infants	Crying, requires oxygen, increased vital signs, expression, sleepless
NIPS (neonatal infant pain scale)	Newborn to 1 year	Facial expression, cry, breathing patterns, arms, legs, state of arousal
NPASS (neonatal pain, agitation, and sedation scale)	Premature infants to 100 days	Crying irritability, behavior state, facial expression, extremities tone, vital signs
FLACC	2 months to 7 years	Face, legs, activity, cry, consolability
COMFORT-B (COMFORT-behavior)	3 months to 18 years, unable to self-report	Alertness, calmness/agitation, respiratory response, physical movement, mean arterial blood pressure, heart rate, muscle tone, facial tension
CHEOPS (Children's Hospital of Eastern Ontario Pain Scale)	1–7 years	Cry, facial, verbal, torso, touch, legs
OUCHER™	3 years and up	Photographs of children's faces with accompanying scale from content to distressed (self-reported)
Wong-Baker faces	3 years and up	Cartoon faces with varying levels of pain (self-reported)
FPS-R (faces pain scale-revised)	4 years and up	Cartoon faces without smiles or tears to avoid happy or sad connotations, respectively
VAS (visual analog scale)d	6 years and up	Finger span scale or word anchors (self-reported)

Even with these standardized scales, the challenges of assessing pain in pediatric patients, and poor validation of specific scales in neonates and infants after cardiac surgery, there is an ongoing development of more objective measurements of pain (Pollak et al. 2019). One such tool is the Analgesia Nociception Index (ANI), which assesses parasympathetic tone by analyzing heart rate variability to infer pain levels. A small prospective observational study of pediatric patients less than 7 years old or with communication disabilities undergoing painful surgery or non-painful procedures such as MRI, which required anesthesia showed a good correlation in pain assessments by ANI with the standardized FLACC (Face, Leg, Activity, Cry, Consolability) behavioral pain assessment tool (Gall et al. 2015). In addition, dynamic facial expression analysis may also provide an automatic pain assessment for infants (Zhi et al. 2018). However, both behavioral and objective assessments may also be limited by factors specific to cardiac surgery, including postoperative use of medications which may affect objective measures of heart rate and blood pressure, as well as sedation and mechanical ventilation, occasionally with neuromuscular blockade, rendering certain components of different assessment tools not applicable. A specific tool for assessing pain in pediatric patients after cardiac surgery which aims to account for sedation and mechanical ventilation is the Cardiac Analgesic Assessment Scale (CAAS), which incorporates objective values for pupillary size, heart rate, blood pressure, and respiratory and motor response, with preassigned values for patients with pacemakers or those treated with neuromuscular blockade; however, this has not been well validated and may not correlate with VAS scores, so its utility is unclear (Pollak et al. 2019; Suominen et al. 2004a). Further development of objective measurements of pain and nociception to overcome these barriers, including machine learning and advanced physiological monitors, may add to the ability to assess pain in pediatric cardiac surgery patients accurately, but currently are limited by resources, cost, and validation in this specific patient population (Pollak et al. 2019).

Current Trends in the Treatment of Acute Pain After Cardiac Surgery

Enhanced Recovery After Surgery (ERAS) and "Fast-Track" Cardiac Surgery

For decades high-dose opioid therapy has been the cornerstone of analgesia for cardiac surgery. However, multiple factors have caused a paradigm shift toward smaller amounts of opioids and increasing the use of non-opioid multimodal analgesics and regional anesthesia techniques. The advent of "fast-track" cardiac anesthesia utilized this approach with goals of shorter time to extubation and decreased ICU and hospital length of stay (Lu et al. 2020). More recently, after widespread use in other surgical fields, ERAS programs have started to permeate into the cardiac surgery realm, incorporating a patient-centered evidence-based approach of preoperative optimization of modifiable risk factors, nutrition, and hydration, as well as goal-directed fluid management and reduction of opioid use, and early mobilization to improve patient outcomes (Noss et al. 2018; Lu et al. 2020; Engelman et al. 2019). There is emerging data that implementing such ERAS pathways for cardiac surgery, explicitly incorporating multimodal analgesics and regional anesthesia techniques, may have beneficial impacts on earlier time to extubation, shorter hospital LOS, and decreased intraoperative opioid use (Grant et al. 2020a, b). Although proven effective in other surgical fields, the complexity and heterogeneity of cardiac surgery patients have thus far impeded the widespread implementation and validation of such pathways in the field.

Minimally Invasive Cardiac Surgery

Paralleling advances in minimally invasive approaches in other surgical fields, including thoracic surgery, there have been advances in minimally invasive cardiac surgery, with goals of faster recovery times and return to baseline function (Parnell and Prince 2018). Surgical

approaches can involve parasternal incisions, minithoracotomies, and ports for video-assisted or robot-assisted procedures. In addition, the transapical transcatheter aortic valve and mitral valve replacements or repairs can be performed with this technique, and regional anesthesia techniques such as paravertebral blocks or serratus anterior plane blocks may prove helpful in this and other minimally invasive approaches, as discussed separately below (Mittnacht et al. 2019). Although these surgical approaches are less invasive than many other procedures requiring full median sternotomy, the same types and sources of pain with their potential negative consequences on recovery as detailed above apply (Malik et al. 2016). In addition, regional anesthetic techniques targeting specific chest wall innervations may be helpful in less invasive procedures such as implantable cardiac devices, including pacemakers or defibrillators (Mittnacht et al. 2019).

Treatment of Pain in Pediatric Cardiac Surgery Patients

An international survey of providers who manage pediatric patients after cardiac surgery revealed a wide range of analgesic approaches, with morphine being the most common analgesic choice, and even within this one medication; however, there was considerable variety in the dosing regimens (Zeilmaker-Roest et al. 2017). Compared to the literature on the treatment of postoperative pain in adult cardiac surgery patients, there is considerably less data and fewer published randomized controlled trials for the pediatric population for several reasons: there are a more significant number of adult patients who undergo cardiac surgery procedures, pediatric trials are not uncommonly discontinued without publication of results due to poor recruitment, there may be less funding available for pediatric trials (Boric et al. 2017). Also, differences in accurately assessing pain in pediatric patients, as detailed above, differing pharmacokinetic and pharmacodynamic properties, and age-related drug licensing make it challenging to translate data in analgesia for adult cardiac surgery patients to pediatric patients (Saini et al. 2020). Currently, broad consensus guidelines are detailing the treatment of pain in children, with emphasis on proper assessment and utilization of multimodal non-opioid therapies, including non-pharmacological interventions (e.g., massage and music therapy, child-life specialist consultation, games, videos, distraction technologies, noise-reduction, sleep and nutrition optimization, reassurance, and comfort), as well as opioid therapies as indicated (Shah and Siu 2019; Playfor et al. 2006). We will address separately below the current trends and evidence for systemic and regional anesthesia therapies for pediatric cardiac surgery patients.

Systemic Therapies

Acetaminophen

Acetaminophen or paracetamol is a cyclooxygenase (COX) inhibitor that acts in the central nervous system to decrease prostaglandin synthesis and likely affects multiple pathways involved in pain, but the exact mechanism of action remains unknown to this day despite decades of use in a wide variety of patients and surgical procedures. Although it acts as a COX inhibitor, it has little to no anti-inflammatory effect or effects on renal perfusion, gastrointestinal (GI) mucosal integrity, or platelet function, and it has a highly safety profile when used in appropriate doses. Pharmacokinetic studies have demonstrated a quicker onset to peak analgesic activity in the IV versus oral formulation (25 compared to 45 min, respectively), whoever both have similar maximum analgesic levels and duration of action (Oscier and Milner 2009). Given a concern for GI absorption in cardiac surgery, even with rectal administration due to altered GI perfusion, the IV route is sometimes preferred in the immediate perioperative period. There is convincing evidence in a mixed surgical cohort that intravenous (IV) acetaminophen can reduce postoperative pain and opioid consumption, with a systematic review suggesting a number needed to treat of four (McNicol et al. 2011). Acetaminophen can

also effectively reduce ipsilateral shoulder pain when used in addition to thoracic epidural analgesia after thoracotomy (Mac et al. 2005). There have been multiple randomized trials investigating the use of IV acetaminophen in adult patients undergoing cardiac surgery, with results including reduced opioid consumption in the first 24 h (Jelacic et al. 2016), reduced pain scores (Mamoun et al. 2016), as well as decreased postoperative delirium, ICU LOS, and breakthrough analgesia use (Subramaniam et al. 2019), but no difference in persistent pain after cardiac surgery (Turan et al. 2017).

Although there is limited data specifically on the use of acetaminophen in pediatric cardiac surgical patients, it is ubiquitously used with few adverse effects or contraindications in children (Saini et al. 2020). Pharmacokinetic studies have shown a lower clearance and higher volume of distribution for acetaminophen after cardiac surgery compared to noncardiac surgery; however, this does not seem to confer any appreciable clinical effect on efficacy or safety (Mian et al. 2019). Interestingly, IV acetaminophen has been associated with transient hypotension, with observational data suggesting that 5% of pediatric patients in a cardiovascular ICU experienced a mean arterial blood pressure decrease of 15% from baseline after a dose (Achuff et al. 2019). A systematic review of IV acetaminophen for cardiac surgery showed a possible signal for decreased cardiac index immediately after administration. Hypotension could have important implications in patients after cardiac surgery where stable hemodynamics are vital; however, the underlying mechanism and clinical significance of such transient hypotension are unclear, and adverse reactions remain extremely rare (Douzjian and Kulik 2017).

In addition to its analgesic and opioid-sparing properties, its effects on lipid peroxidation have been of interest specifically for patients undergoing CPB. Erythrocytes are lysed during CPB, and acetaminophen may attenuate hemeprotein-mediated lipid peroxidation and preserve kidney function in animal studies. Acute kidney injury is associated with increased LOS, higher morbidity and mortality, and cardiac surgery patients, including pediatric patients, may be at higher risk than other critically ill patients (Van Driest et al. 2018). A retrospective observational study of pediatric cardiac surgery patients showed an association with lower incidence of acute kidney injury in patients who received acetaminophen, which could possibly be related to acetaminophen decreasing oxidation of free hemoglobin, which is nephrotoxic (Van Driest et al. 2018). However, although acetaminophen has been shown to reduce a specific byproduct of lipid peroxidation in patients undergoing CPB, other serum markers and urinary markers of lipid peroxidation were not reduced, and the clinical significance of this effect of acetaminophen is unclear (Billings et al. 2015; Simpson et al. 2014).

Non-Steroidal Anti-Inflammatory Drugs

Non-steroidal anti-inflammatory drugs (NSAIDs) are a class of COX inhibitors with anti-inflammatory and analgesic properties. Multiple isoforms exist, with COX-1 constitutively expressed with effects on renal perfusion, GI mucosal integrity, and platelet function, and COX-2 induced in the CNS during inflammatory responses. While non-specific NSAIDs, including ketorolac, may have harmful effects on kidney function, GI bleeding, and platelet function, COX-2 selective drugs, including celecoxib, have much less of an effect on platelet function. NSAIDs have proven efficacy as part of multimodal analgesic approaches and can help to reduce opioid consumption in a wide range of surgeries (Martinez et al. 2017). Additionally, the combination of NSAIDs with acetaminophen seems to have synergistic analgesic effects (Ong et al. 2010). Although NSAIDs, including ketorolac, are commonly used for acute postoperative pain in surgical patients, their routine use in cardiac surgery patients is not widespread due to risks of and worsened outcomes associated with bleeding and acute kidney injury in a vulnerable population. While data on COX-2 inhibitors in cardiac surgery is limited due to concerns for

increased risk of adverse cardiovascular events related to these drugs after cardiac surgery, celecoxib can have beneficial effects on lower pain scores and improved patient satisfaction after thoracotomy (Senard et al. 2010). While the use of NSAIDs after adult cardiac surgery is limited, a large retrospective analysis of over 1300 cardiac surgery patients, 488 of whom received ketorolac postoperatively, failed to find any increased incidence of bleeding cardiovascular events, including myocardial infarction or cerebrovascular accident; however, patients who received ketorolac were younger, had a better preoperative renal function, and underwent less complex operations (Oliveri et al. 2014). This suggests that ketorolac may be a safe option in select low-risk patients after cardiac surgery; however, caution is warranted given the lack of prospective randomized data in this population.

Ketorolac is commonly used for short-term analgesia for severe pain in children over 2 years of age and can provide comparable analgesia to morphine in critically ill children (Saini et al. 2020). It may also be more efficacious than acetaminophen for surgical pain after congenital heart surgery in pediatric patients (Amini et al. 2016). The safety of NSAIDs in infants and young children has been an area of interest, with limited data as many studies in children are retrospective, have small sample sizes, and often exclude many patients with congenital heart disease who may be at the highest risk for adverse effects related to NSAIDs (Saini et al. 2020). In addition, ketorolac use in infants less than 21 days old or 37 weeks corrected gestational age imposes a significantly increased risk of bleeding and should be avoided in this age range (Aldrink et al. 2011). A small retrospective study of 53 patients who received NSAIDs after cardiac surgery, 11 of whom were less than 1 month old, revealed that all patients included did have a rise in blood urea nitrogen and creatinine levels but remained within normal limits and returned to baseline, however, given the significant increased risk of morbidity with AKI and the unknown long-term consequences of transient decreases in renal function, caution is warranted in young patients and those at risk for AKI due to surgical or patient factors (Moffett et al. 2006). In older patients ranging from 1 month to 18 years, retrospective analysis of NSAID use did not reveal any significant increase in bleeding or renal dysfunction and did show a significant reduction in opioid consumption after cardiac surgery (Savva et al. 2019). Similarly, a more extensive retrospective study of 248 pediatric cardiac surgery patients, 108 of whom received ketorolac, did not show any significant change from baseline creatinine and did have an opioid-sparing effect (Inoue et al. 2009). There is limited prospective data from a randomized trial of 70 infants ranging from two and one half months to 14 years old who received either standard of care with or without ketorolac for 36–48 h postoperatively, which did not show any significant differences in adverse effects including bleeding, but also no differences in secondary outcomes including analgesia (Gupta et al. 2004). Altogether, the available data suggests that in certain low-risk pediatric patients, NSAIDs may be beneficial and safe; however, caution should be used in higher-risk or very young patients.

Gabapentinoids

Gabapentin and pregabalin are a class of voltage-gated calcium channel blockers with analgesic properties resulting from decreased excitatory neurotransmitter release in the dorsal horn and reduced pain signal transmission, potentially reducing central sensitization (Chincholkar 2018). Although both medications have been shown to reduce postoperative pain and opioid requirements in a wide range of surgeries, the clinical significance and benefits versus risks are controversial, with one large systematic review suggesting reduced pain and opioid consumption (Doleman et al. 2015), and a more recent large systematic review showing minor statistically significant differences in pain scores but questionable clinical significance (Verret et al. 2020). Both gabapentin and pregabalin may cause sedation (Doleman et al. 2015; Mishriky et al. 2015). Although they do not have intrinsic effects on respiratory depression, when

used in combination with opioids, they may cause respiratory depression, especially in older patients (Cavalcante et al. 2017). Given that neuropathic pain likely plays a role in acute postoperative pain in cardiac surgery patients, gabapentinoids have been used as part of multimodal and ERAS strategies for cardiac surgery patients. A small systematic review of gabapentin and pregabalin use in cardiac surgery patients failed to find sufficient evidence to recommend the routine use of these medications for cardiac surgery, with mixed results of potentially lower pain scores but inconsistent effects on postoperative opioid consumption (Maitra et al. 2017). A small prospective trial of perioperative pregabalin therapy for off-pump coronary artery bypass grafting showed significant improvement in the primary endpoint of global quality of recovery scores with improved emotional state, physical comfort, and pain, but also increased dizziness (Borde et al. 2017). Two other prospective trials for gabapentin use for cardiac surgery had conflicting results, with one trial showing no difference in pain, opioid consumption, or patient-perceived quality of recovery (Rapchuk et al. 2010), with the other trial showing potential reduced pain and opioid requirements, but also increased sedation and need for mechanical ventilation (Menda et al. 2010). Similarly, a randomized trial comparing pregabalin to a placebo for cardiac surgery showed decreased pain scores but no effect on opioid consumption (Ziyaeifard et al. 2015). Given their possible prevention of central sensitization and neuropathic contributions to chronic pain, these medications have also been of interest to prevent chronic pain after cardiac surgery; however, the data is limited and there does not seem to be any clinically significant effect on chronic pain (Ucak et al. 2011; Bouzia et al. 2017).

There is much less data on the use of gabapentin or pregabalin in pediatric patients; however, a retrospective review of 22 critically ill neonates and infants showed possible benefits of improved standardized pain scores, decreased analgesic, and sedative requirements, without evidence of adverse effects (Sacha et al. 2017).

Lidocaine

Lidocaine is a commonly used local anesthetic and antiarrhythmic, which has predominantly sodium channel blocking properties, but may also have effects including attenuation of central sensitization, anti-inflammatory properties, reduced CNS pain signaling, and potential cardioprotective effects against myocardial ischemia and reperfusion injury in animal models (Noss et al. 2018; Lee et al. 2011). As a local anesthetic, it also poses a risk of systemic toxicity, including cardiac depression arrhythmia. Although there is data suggesting it has analgesic and opioid-sparing benefits in abdominal surgery, there is limited data on the benefits and safety of IV lidocaine, specifically in cardiac surgery (Noss et al. 2018). One randomized trial of 100 patients undergoing CABG failed to show any difference in opioid consumption or other clinical outcomes in patients that received intraoperative lidocaine infusions compared to placebo (Insler et al. 1995). Given its potential protective effects of blocking sodium channels and reducing intracellular calcium loading and generation of reactive oxygen species in animal models, a prospective trial investigated its effect on myocardial injury in off-pump coronary artery bypass grafting. This study randomized 99 patients to intraoperative lidocaine versus saline and measured cardiac biomarkers, with results showing reduced troponin I and CK-MB values, suggesting that lidocaine may have a role in reducing myocardial injury; however, the clinical implications of this is not clear (Lee et al. 2011). There are no fundamental published data on the use of intravenous lidocaine for pediatric cardiac surgery.

Corticosteroids

The perioperative use of glucocorticoids, including dexamethasone, is well-established in both adult and pediatric patients, mainly for benefits including postoperative nausea and vomiting prophylaxis, and anti-inflammatory effects; however, multiple large systematic reviews have also revealed additional benefits including reduced

pain, shorter post-anesthesia care unit (PACU) length of stay (LOS), and lower opioid requirements (De Oliveira Jr et al. 2011; Waldron et al. 2013). Although hyperglycemia is a known effect of glucocorticoid use, there is no evidence suggesting significant increases in the risk of infections or delayed wound healing. Given the massive inflammatory response related to cardiac surgery and CPB, corticosteroids have been an area of interest as a means to potentially blunt this response and its negative consequences (Murphy et al. 2013). A large randomized trial of over 400 patients undergoing cardiac surgery with CPB treated with high-dose dexamethasone failed to find any difference in the primary endpoint, which included death, myocardial infarction, stroke, renal failure, or respiratory failure within 30 days; interestingly, however, patients who received dexamethasone had a lower incidence of infection, shorter duration of mechanical ventilation, shorter ICU and hospital LOS, and as expected higher perioperative glucose levels (Dieleman et al. 2012). Similar results from an even more extensive international study of over 7000 patients who received high-dose methylprednisolone for cardiac surgery failed to find any decrease in the risk of death or significant morbidity (Whitlock et al. 2015). Although there is no data explicitly looking at analgesic benefits of corticosteroids in adult or pediatric cardiac surgery patients, given its potential benefits on analgesia, postoperative nausea and vomiting, and reducing inflammation without significant risk for adverse effects other than hyperglycemia, it is reasonable to consider corticosteroids in these patient populations.

Alpha-2 Adrenergic Agonists

Alpha-2 adrenergic receptor agonists, including dexmedetomidine and clonidine, have analgesic and sedative properties in addition to decreasing sympathetic output. In fact, dexmedetomidine has many beneficial properties for cardiac surgery patients, including analgesia, reduced delirium, favorable hemodynamic responses, attenuation of sympathetically driven hypertension and tachycardia, and protection against ischemia and reperfusion injury in animal models (Ji et al. 2013). In addition, multiple retrospective analyses of more than 2000 patients who had undergone cardiac surgery showed that dexmedetomidine is associated with reduced mortality up to 1 year and decreased complications, including delirium (Ji et al. 2013; Ji et al. 2014).

Dexmedetomidine and clonidine are both used in pediatric cardiac surgery patients as well. A prospective cohort study comparing 32 pediatric patients undergoing cardiothoracic procedures who were treated with dexmedetomidine to 20 patients who did not receive dexmedetomidine showed significant reductions in postoperative arrhythmias including ventricular tachycardia and supraventricular tachycardia, and these patients also required less rescue fentanyl and antihypertensive medications postoperatively, suggesting that dexmedetomidine may have beneficial hemodynamic and analgesic properties for pediatric cardiac surgery patients (Chrysostomou et al. 2011). A systematic review of randomized and observational trials investigating dexmedetomidine use for more than 2000 pediatric patients undergoing congenital heart disease surgery showed multiple benefits, including lower postoperative opioid consumption, lower risk of delirium, and shorter duration of mechanical ventilation. However, there was also an increased risk for bradycardia and hypotension (Pan et al. 2016). Interestingly, a large systematic review of factors that may prevent AKI in pediatric cardiac surgery patients identified dexmedetomidine and acetaminophen both as having potential protective effects, possibly through attenuation of inflammatory response and ischemia/reperfusion injuries, although the mechanism behind the association and its clinical implications is not known (Bellos et al. 2019). Taken together, this suggests that dexmedetomidine may have multiple benefits for postoperative management of pediatric congenital heart surgery patients; however, further prospective studies will be needed to determine specific populations that may be more at risk for adverse effects. Clonidine, another alpha-2 adrenergic receptor agonist, has also been used for pediatric cardiac surgery patients

for its sedative, analgesic, and hemodynamic properties, as well as to aid in weaning from opioid infusions to reduce withdrawal symptoms. Indeed, there is retrospective data that for infants who had undergone cardiac surgery and required prolonged sedation and analgesia with opioids postoperatively, clonidine infusions can facilitate wean from opioids and provide stable hemodynamics without significant adverse effects (Pohl-Schickinger et al. 2008).

N-Methyl-D-Aspartate (NMDA) Receptor Antagonists

The NMDA receptor is involved in excitatory neurotransmission, and activation during painful stimulation and inflammatory responses may lead to central sensitization, a phenomenon in which tissue trauma and nociceptive signaling leads to increased excitability in the CNS and can result in hyperalgesia (amplified pain to noxious stimuli) and allodynia (pain from a normally benign stimulus) (Petrenko et al. 2003). NMDA antagonists have intrinsic analgesic effects, may have opioid-sparing effects, and may prevent or attenuate central sensitization. The two most commonly used NMDA antagonists that have been studied in cardiac surgery are ketamine and magnesium. Methadone, which also acts as an opioid receptor agonist, also has NMDA antagonist activity and is discussed separately below.

Ketamine

Ketamine is an NMDA receptor agonist with potent analgesic activity when used in subhypnotic doses and can also induce a state of general anesthesia. In addition to analgesia, it can cause sedation and hypnosis and increased sympathetic activity without significant respiratory depression. The most common and unpleasant adverse effects include hallucinations and nightmares, especially in older adults (Avidan et al. 2017). In addition to analgesia, NMDA blockade from ketamine may have beneficial effects of reducing opioid tolerance, potentiate the analgesic effects of concurrent opioid therapy, reduce central sensitization, and may have anti-inflammatory effects (Laskowski et al. 2011; Guirimand et al. 2000; Sleigh et al. 2014). Because ketamine can also cause sympathetic activation, it may cause less hypotension on induction of anesthesia in cardiac surgery patient compared to propofol in patients with normal systolic function (Basagan-Mogol et al. 2010). However, when combined with propofol, ketamine still causes more hemodynamic changes including hypotension requiring vasopressors compared to etomidate in patients with reduced left ventricular systolic function (Baradari et al. 2017). A randomized trial of adult patients undergoing coronary artery bypass grafting treated with intraoperative ketamine versus placebo showed lower opioid consumption in the first 48 h and higher patient satisfaction, suggesting that intraoperative ketamine can be helpful for postoperative analgesia after cardiac surgery in adults (Lahtinen et al. 2004). However, a more recent similar prospective trial failed to show any effect on postoperative pain or opioid requirements after cardiac surgery (Cameron et al. 2020). A small study investigating ketamine use for thoracotomy in patients undergoing CABG for lung tumor resection showed lower pain scores and opioid consumption in the immediate postoperative period; however, no data were collected beyond 4 h postoperatively, and the effect on other clinical outcomes is not clear (Nesher et al. 2009). Although the data on ketamine's effect on postoperative pain and opioid consumption is limited and mixed, there is also prospective data to suggest that ketamine may attenuate the inflammatory response related to cardiac surgery and CPB, with lower measured levels of proinflammatory markers and higher levels of anti-inflammatory markers in patients who received ketamine; this suggests that ketamine may have beneficial anti-inflammatory effects for patients undergoing CPB, but the clinical significance of this and effect on patient outcomes is unclear (Welters et al. 2011). The data on ketamine for pediatric cardiac surgery patients is even more limited; however, a large systematic review of the use of ketamine for perioperative pain in pediatric patients, although limited by significant heterogeneity, did find evidence of

reduced immediate postoperative pain (Dahmani et al. 2011).

Magnesium

Magnesium also has antagonistic activity at NMDA receptors, and although the data are mixed, it may reduce pain scores and opioid requirements in noncardiac surgical patients without significant adverse effects, as shown in multiple large systematic reviews (Albrecht et al. 2013; De Oliveira et al. 2013; Lysakowski et al. 2007). In addition to the possible benefits of analgesia and prevention of central sensitization, magnesium may also attenuate the inflammatory response to cardiopulmonary bypass (Noss et al. 2018). For cardiac surgery, although there is limited data in adults and no prospective investigations in pediatric patients, one prospective randomized trial of adult patients undergoing CABG treated with magnesium sulfate versus placebo did show evidence of lower pain scores and opioid consumption within the first 24 h as well as shorter time to extubation, suggesting that magnesium may be a useful non-opioid adjunct without significant risk in cardiac surgical patients (Ferasatkish et al. 2008).

Opioids

High-dose opioid therapy has been a mainstay of cardiac surgery postoperative analgesia in children and adults, with postulated benefits of reducing the negative consequences of pain and the surgical stress response detailed above (Humphreys et al. 2005). However, opioids are not without negative adverse effects, including sedation, respiratory depression with risk of prolonged mechanical ventilation and pulmonary complications, ileus, tolerance, and dependence (Bigeleisen and Goehner 2015). Also, there are concerns for potential long-term effects of opioid therapy in pediatric patients, as there is some evidence of long-term negative consequences, including behavior changes, memory, and synaptic neuroplasticity with neonatal opioid therapy in animal models and repeated morphine exposures in children (Pollak et al. 2019). The mu opioid receptor is the major opioid receptor involved in analgesia and is located in multiple sites in the CNS, including the dorsal root ganglion and periaqueductal gray matter, and mu opioid receptor agonists exert their analgesic effect by decreasing excitability and modulating pain pathways.

A variety of opioids are utilized after cardiac surgery, each with specific properties that may be beneficial for certain procedures or time points in the perioperative period. Morphine is commonly used for intraoperative and post-operative analgesia. In addition to the above opioid-related adverse effects, morphine may cause histamine release with itching and vasodilation, and has active metabolites that may accumulate and increase the risk of adverse effects with impaired renal function. Hydromorphone is more potent than morphine, lacks histamine release, and is safer with impaired renal function. Fentanyl is more lipid-soluble than morphine or hydromorphone and therefore has a more rapid onset and shorter duration of action and lacks significant effects on histamine release. Remifentanil is a pure mu opioid agonist with a very short half-life due to metabolism by plasma and tissue esterases, allowing for dense analgesia and blunting of sympathetic responses to noxious stimuli without prolonged sedation or respiratory depression; however, it can be associated with acute opioid tolerance and hyperalgesia (Playfor et al. 2006). Patient-controlled analgesia (PCA) allows patients to self-administer a bolus dose of analgesic on demand, with a prespecified dose, lockout time, and hourly maximum, with or without a basal infusion and allows for improved analgesia while minimizing adverse effects (Jayakumar et al. 2019).

Postoperative pain in pediatric patients is commonly managed with opioids, including infusions with or without intermittent dosing, most commonly with morphine or fentanyl (Playfor et al. 2006; Diaz 2006). However, prospective data shows that continuous morphine infusions after pediatric cardiac surgery does not improve pain control compared to intermittent dosing and may actually be associated

with increased opioid consumption and length of stay (LOS) (Penk et al. 2018). A prospective observational study of pediatric patients undergoing surgery for congenital heart disease repair showed that rescue analgesia with morphine in the first 24 h postoperatively with increasing measured concentrations of morphine did not reduce the likelihood of needing further rescue doses, which suggests that the addition of other analgesics may be more beneficial than simply higher or more frequent doses of morphine for postoperative pain pediatric congenital heart disease patients (de Hoogd et al. 2021). Morphine may also increase the risk of respiratory depression under 3 months of age at standard doses due to increased CNS penetration from an immature blood-brain barrier (Shah and Siu 2019). Infants and young children with congenital heart disease may also exhibit different pharmacokinetics after congenital heart surgery, with a wide variety in metabolism and clearance and risk of less clearance due to alterations in hepatic blood flow in the perioperative period and accumulation of active metabolites with changes in renal function (Elkomy et al. 2016; Wolf and Jackman 2011). PCA can be utilized in some patients 5 years and older and may provide better analgesia, patient autonomy, and decreased fear and anxiety (Shah and Siu 2019). However, young children or those with cognitive impairment or developmental delay may be unable to effectively use PCA, and as-needed doses or infusions may lead to less optimal pain control, with less control of promptly treating dynamic changes in pain or overtreating transient pain exacerbations. Parent-/nurse-controlled analgesia (PNCA) or PCA by proxy with appropriate education on risks and benefits may offer an effective approach to opioid therapy but may increase the risk of overdose as it bypasses the safety benefit of PCA whereby patients are unable to self-administer additional doses if too sedated, potentially leading to increased risk of respiratory depression and need for naloxone opioid antagonist therapy (Shah and Siu 2019; Monitto et al. 2000).

Methadone

Methadone has multiple mechanisms of providing analgesia for acute pain, including mu opioid receptor agonism and NMDA antagonism. It has a long duration of action, ranging from 24–36 h after a single dose, and may provide a more stable background level of analgesia in the postoperative period compared to intermittent dosing, which results in waxing and waning levels of analgesia with brief periods of optimal analgesia. Through its NMDA antagonism, it may also prevent central sensitization and reduce the development of opioid tolerance (Murphy et al. 2020; Iguidbashian et al. 2020). Given these potential advantages over pure mu opioid receptor agonist infusion or intermittent dosing, it has successfully been used as an effective analgesic for major surgeries, including spine and cardiac surgery. A randomized trial of intraoperative single-dose methadone compared to fentanyl showed significant reductions in 24-h opioid requirements, pain scores with coughing, and improved patient-perceived quality of pain management without any increased incidence of opioid-related adverse effects, suggesting that intraoperative methadone can be an effective analgesic strategy and reduce patient experience, pain, and opioid requirements compared to traditional high-dose opioid therapy (Murphy et al. 2015). More recently, a preplanned analysis of long-term outcomes for patients who had undergone spine or cardiac surgery and were treated with intraoperative methadone therapy showed a continued effect of reduced pain at 1 month for the cardiac surgery group. Methadone may have preventive analgesia effects, where the benefits outlast the expected duration of action of the medication, potentially related to preventing central sensitization (Murphy et al. 2020). Methadone has also been successfully used in pediatric cardiac surgery patients. A retrospective study of pediatric cardiac surgery patients treated with methadone intraoperatively showed a lower need for intraoperative analgesics and sedatives, as well as lower opioid consumption in the first 24 h postoperatively in non-neonates and lower sedation scores in the first week postoperatively, suggesting that methadone is a safe and efficacious tool for analgesia in this patient population and may have

beneficial effects on lowering opioid requirements (Barnett et al. 2020). Similarly, a recent retrospective case series of pediatric cardiac surgery patients treated with intraoperative methadone as part of a multimodal analgesic approach without other opioids showed adequate pain control immediately postoperatively without adverse effects, suggesting that methadone is safe in this population (Iguidbashian et al. 2020). However, larger and prospective studies will be needed to investigate the efficacy of methadone compared to other approaches and its potential effects on other clinical outcomes in pediatric cardiac surgery patients.

Regional Anesthesia for Cardiac Surgery

Regional anesthesia techniques offer many potential advantages as part of a multimodal analgesic approach to cardiac surgery, including optimal analgesia, reduced need for opioid or other sedating medications, facilitation of rapid extubation with improved ventilatory mechanics, improved hemodynamics, and reduced stress response in the perioperative period (Peterson et al. 2000). Regional anesthesia for cardiac surgery encompasses a wide range of techniques, and with the expansion of ultrasound-guided regional anesthesia and development of various technically easy fascial plane blocks with lower risks of bleeding or complications compared to neuraxial techniques, this increased repertoire of pain management options will only expand the tools available for the perioperative acute pain management of both adult and pediatric congenital heart surgery patients (Monahan et al. 2019; Liu et al. 2019). The following sections will summarize the techniques that have applications in cardiac surgery, following the most recent consensus nomenclature and classification (Tables 2 and 3, Fig. 2) (El-Boghdadly et al. 2021).

Neuraxial Anesthesia/Analgesia

Neuraxial techniques including epidural, spinal, and caudal anesthesia and analgesia have been used for decades in pediatric and adult patients undergoing cardiac surgery. High thoracic blockade allows stable hemodynamics without response to surgical stimulus and a beneficial myocardial oxygen supply and demand balance. Neuraxial blockade provides both surgical anesthesia and postoperative analgesia and may also attenuate cardiac surgery's neuroendocrine and inflammatory response, which can negatively affect patients, as described earlier (Chaney 2006; Kowalewski et al. 2011). A retrospective review of various neuraxial techniques in pediatric cardiac surgery patients showed excellent postoperative analgesia, high rates of early extubation, and no serious adverse effects, suggesting that neuraxial anesthesia may be a safe and effective option for analgesia in this population (Peterson et al. 2000). However, despite the long history of neuraxial techniques for cardiac surgery in both adults and children, their utility and safety have remained controversial due to the risk of devastating neurological damage related to epidural hematoma, which may be increased with systemic heparinization required for cardiopulmonary bypass.

Thoracic Epidural and Caudal Anesthesia/Analgesia

Thoracic epidural analgesia (TEA) involves the deposition of local anesthetics, often in combination with opioids, into the epidural space which is bordered by the ligamentum flavum posteriorly and the dura mater anteriorly. This space contains the spinal nerves with their dorsal and ventral rami and the sympathetic chain. The neural blockade at this site leads to bilateral segmental sensory blockade as well as a visceral nociceptive blockade from effects on sympathetic fibers. Epidural catheter placement allows for ongoing analgesia in the postoperative period as well. Sympathetic blockade by TEA may attenuate the stress response in the perioperative period and potentially reduce the risk of adverse cardiovascular events (Freise and Van Aken 2011). In a mixed surgical cohort, TEA is associated with reduced mortality and lower incidence of dysrhythmias, deep venous thrombosis, respiratory depression, and atelectasis

Table 2 Regional anesthesia techniques for cardiac surgery. Regional anesthesia techniques used for thoracic and cardiac surgery, organized by anatomic region of the block (neuraxial, paraspinal, and chest wall), relevant anatomy, and targeted nervous structures and resultant sensory blockade

Region and name of block	Anatomic location	Nerves affected/sensory distribution
Neuraxial		
Thoracic epidural Anesthesia/ analgesia (TEA)	Epidural between ligamentum flavum and dura mater	Spinal nerve roots and sympathetic chain, diffusion to intrathecal space/bilateral segmental and visceral
Spinal anesthesia	Intrathecal	Spinal nerve roots, spinal cord/ bilateral below level of block, visceral
Caudal anesthesia/analgesia	Epidural space accessed through sacrococcygeal ligament at sacral hiatus	Spinal nerve roots and sympathetic chain, diffusion to intrathecal space/ bilateral segmental and visceral
Paraspinal		
Paravertebral block (PVB)	Paravertebral space between superior costotransverse ligament and parietal pleura	Spinal nerve dorsal and ventral rami and sympathetic chain/ipsilateral segmental and visceral
Erector Spinae plane (ESP) block	Plane between erector spinae muscles and transverse process	Dorsal rami, possible spread to paravertebral space affecting ventral rami T2–T9 and sympathetic chain/ipsilateral posterior and possibly lateral and anterior chest wall and visceral
Chest wall		
Superficial serratus anterior plane (SAP) block	Plane superficial to serratus anterior muscles	Lateral cutaneous branch of intercostal nerves T3–T9/lateral chest wall
Deep serratus anterior plane (SAP) block	Plane between posterior surface of serratus anterior muscle and rib	Lateral cutaneous branch of intercostal nerves T3–T9/lateral chest wall
Superficial parasternal intercostal plane (PIP) block	Plane superficial to internal intercostal muscles and ribs and deep to pectoralis major muscle	Anterior cutaneous branch of intercostal nerve/anterior chest wall and sternum
Deep parasternal intercostal plane (PIP) block	Plane between internal intercostal and transversus thoracis muscles	Anterior cutaneous branch of intercostal nerve/anterior chest wall and sternum
Interpectoral plane (IPP) block	Plane between pectoralis major and pectoralis minor muscles	Medial and lateral pectoral nerves and lateral cutaneous branches of T2–T6/ upper anterolateral chest wall
Pectoserratus plane (PSP) block	Plane between the pectoralis minor and serratus anterior muscles	Lateral cutaneous branches of T2–T6/upper anterolateral chest wall

Table 3 Regional anesthesia options for specific cardiac surgical approaches. Includes specific surgical approaches/ incisions with their associated sensory innervation and regional anesthetic techniques that may be effective in blocking pain signaling for each approach

Surgical approach	Innervation	Regional anesthesia options
Sternotomy	Anterior cutaneous branches of intercostal nerves	TEA, bilateral PVB, ESP block, PIP block, or IPP block
Thoracotomy	Intercostal nerves and possibly dorsal rami of spinal nerves	TEA, PVB, ESP block
Minimally invasive anterolateral minithoracotomy	Lateral and anterior cutaneous branches of intercostal nerves	TEA, PVB, ESP, SAP, or combination of PIP, IPP, and/or PSP blocks
Transapical	Lateral cutaneous branches of intercostal nerves	TEA, PVB, ESP block, SAP block

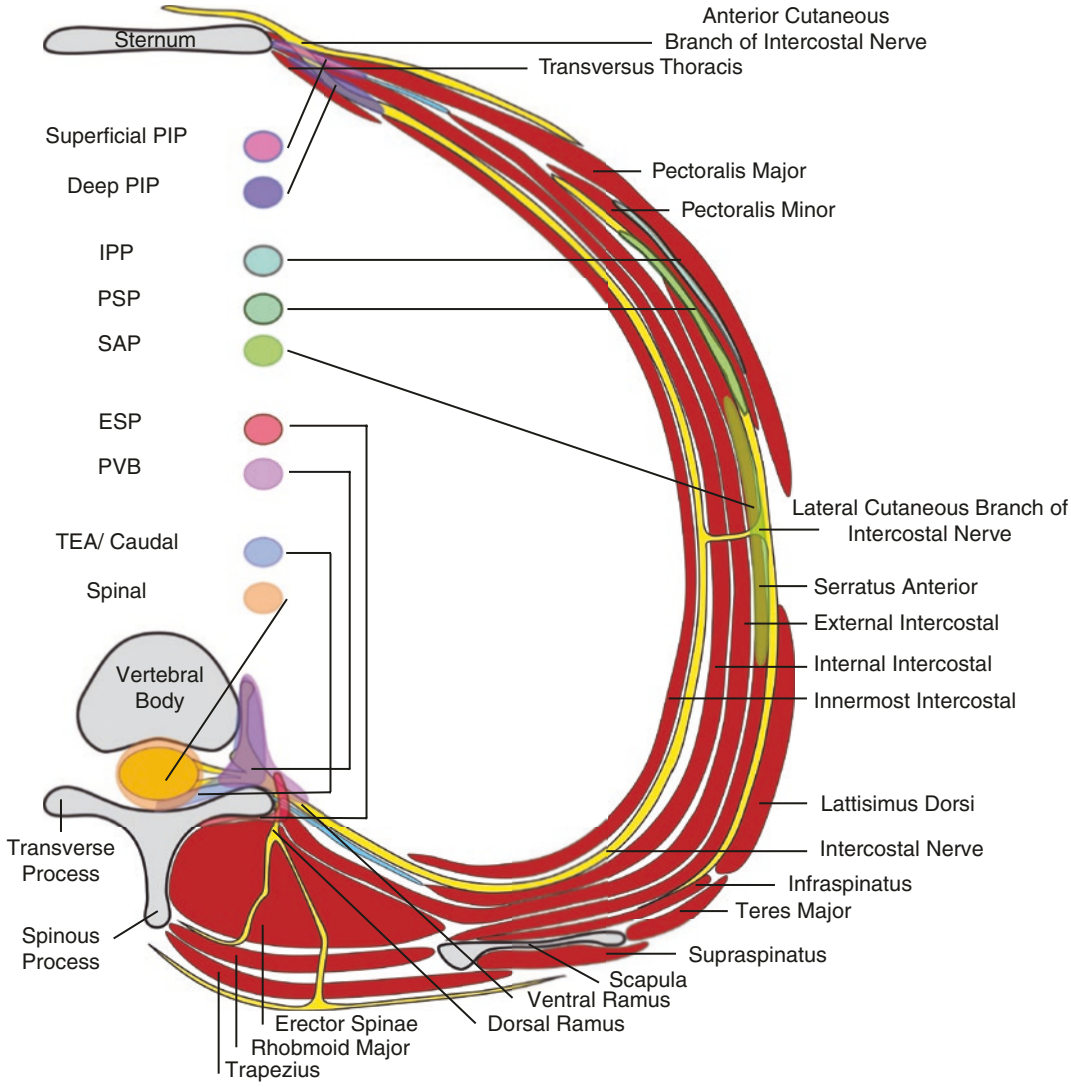

Fig. 2 Sites of action for regional anesthesia techniques for cardiac surgery. Unilateral axial cross-section at the level of T5 with relevant muscle (red), bone (gray), and nervous (yellow) strucutes. Sites of local anesthetic deposition and blockade of relevant nerves are depicted for the neuraxial (TEA/caudal, spinal), paraspinal (PVB, ESP), and chest wall (superficial and deep PIP, IPP, PSP, and SAP) blocks

(Pöpping et al. 2014). Indeed, compared to systemic opioids, neuraxial opioids and local anesthetics may have a lower risk of atelectasis and reduced pulmonary complications (Ballantyne et al. 1998; Pöpping et al. 2008). Common adverse effects of TEAf include hypotension related to the sympathetic blockade, potentially bradycardia from high TEA affecting the cardiac accelerator fibers of T1–T4, urinary retention, and pruritis related to opioids (Pöpping et al. 2008). Rare but serious complications include infection, which could lead to epidural abscess or meningitis, and more pertinent to cardiac surgery given the frequent need for systemic anticoagulation and antiplatelet therapy, bleeding causing epidural hematoma with resultant neuraxial compression and paralysis, both of which could require urgent surgical intervention. The risks of neuraxial techniques for cardiac surgery is discussed separately below.

For cardiac surgery requiring sternotomy, high TEA covers the first five thoracic segments that innervate the sternum, with the expected sympathectomy and blockade of cardiac sympathetic fibers. This causes a favorable benefit for myocardial oxygen supply and demand, with decreased systemic vascular resistance, increased myocardial perfusion, and decreased myocardia oxygen demand, and may the risk of perioperative arrhythmia and ischemia (Caruso et al. 2019; Devarajan et al. 2021; Jakobsen et al. 2012). In fact, a randomized trial of low-to-moderate risk adult patients undergoing cardiac surgery showed higher cardiac index and stroke volume index and higher central venous oxygen levels despite no significant changes in heart rate in patients receiving TEA, suggesting that TEA can improve cardiac performance (Jakobsen et al. 2012). High TEA has even been used as the primary anesthetic for awake cardiac surgery (Bottio et al. 2007). There have been multiple systematic reviews of the safety and efficacy of TEA for cardiac surgery (Devarajan et al. 2021), with evidence of potential reductions in opioid consumption, pain, arrhythmias, respiratory complications, stroke, and ICU LOS, with two of these reviews identifying a reduction in mortality, with a quoted number needed to treat of 70 (Liu et al. 2004; Svircevic et al. 2011; Zhang et al. 2015; Landoni et al. 2015). A more recent Cochrane systematic review of 69 trails and almost 5000 patients showed similar results, with evidence for reduced risk of MI, respiratory depression, arrhythmias, duration of mechanical ventilation, static and dynamic pain up to 3 days postoperatively, but had no effect on mortality, and was associated with increased risk of hypotension and need for vasopressor or inotrope support (Guay and Kopp 2019). Compared to PCA, TEA may lead to a shorter extubation time and lower anesthetic consumption (Hansdottir et al. 2006).

Epidural analgesia is also used for pediatric patients undergoing cardiac surgery. A retrospective review of 750 patients, 52% of whom were less than 1 year old and 75% of whom underwent CPB revealed no neurological complications and suggested that TEA for pediatric cardiac surgery patients can be a safe option and provide stable analgesia without significant risk of complications (Thammasitboon et al. 2010). Another group that routinely uses neuraxial anesthesia for pediatric cardiac surgery patients published a retrospective review including 25 patients that received TEA, all of whom were successfully extubated in the operating room and did not experience any adverse effects (Hammer et al. 2000). Caudal approaches to epidural blocks are more common in children given their easily palpable sacral hiatus landmarks and thinner sacrococcygeal ligament. A systematic review of caudal anesthesia in over 2000 pediatric cardiac surgery patients revealed a high level of heterogeneity among studies (with caudal medications including various opioids, bupivacaine, and dexmedetomidine) with poor quality data, but possible benefits including early extubation, improved pain, more stable hemodynamics, and a reduced LOS (Maharramova and Taylor 2019). One retrospective review of 199 pediatric patients who had undergone cardiac surgery, 86 of whom received caudal bupivacaine, morphine, and clonidine injections, showed decreased intraoperative opioids without clear differences in postoperative pain scores or opioid consumption; however, these results are limited by their small sample size, retrospective nature, and unclear effect on other important clinical outcomes (Nguyen et al. 2016). As the duration of action of single-shot caudal injections is limited by the pharmacokinetics of epidural medications, adjuncts including alpha-2 agonists are sometimes used for various regional anesthesia techniques to prolong the block's duration. In a small prospective randomized trial of pediatric cardiac surgery patients, single-shot caudal anesthesia with bupivacaine and either fentanyl or dexmedetomidine was compared, revealing lower pain scores within the first 8 hours, as well as attenuation of increased cortisol and glucose levels, with significant decreases in hemodynamic parameters including heart rate and blood pressure with dexmedetomidine. Although it is unclear if dexmedetomidine, in this case, had any effect on the duration of analgesia postoperatively, it suggests that caudal dexmedetomidine may have benefits of attenuating the stress response and providing superior early analgesia compared to fentanyl, with additional effects of reduced heart rate and blood pressure (Nasr and Abdelhamid 2013).

Spinal Anesthesia

Spinal anesthesia for cardiac surgery has also been used successfully in adult and pediatric cardiac surgery patients, with the postulated benefit of attenuated stress response and facilitation of early extubation. Although limited, there is some data examining the safety and efficacy of spinal anesthesia in adult cardiac surgery patients. A retrospective propensity-matched cohort study of 920 cardiac surgery patients who received intrathecal morphine matched with similar patients who showed no evidence of compilations from spinal anesthesia, and notably a significantly reduced odds ratio for postoperative pulmonary complications, suggesting that intrathecal morphine may improve analgesia, reduce splinting and atelectasis, and reduced the risk of postoperative pulmonary complications for adult cardiac surgery patients (Ellenberger et al. 2017). Another prospective trial of adults undergoing cardiac surgery randomized patients to intrathecal bupivacaine versus placebo, with results indicating less beta-adrenoreceptor dysfunction in the atria and lower serum stress hormones including epinephrine, norepinephrine, and cortisol, as well as higher cardiac index, suggesting that high spinal anesthesia in adults may attenuate the stress response and preserve cardiac function during adult cardiac surgery (Diaz 2006; Lee et al. 2003).

In the same study mentioned above that reviewed fast-track pediatric cardiac surgery patients who had TEA, a separate group who had spinal anesthesia also were all successfully extubated in the operating room but did require more sedative and analgesic interventions compared to TEA, possibly due to the ability to repeatedly dose or run a continuous infusion through the epidural catheter compared to single-shot tetracaine and morphine intrathecal injection (Hammer et al. 2000). There are prospective data from a randomized trial of pediatric cardiac surgery patients showing that intrathecal morphine can delay the need for first postoperative morphine dosing and reduce the overall postoperative opioid requirements (Suominen et al. 2004b). Similarly, a later randomized trial investigating spinal anesthesia for fast-track pediatric cardiac surgery showed that patients who received spinal anesthesia with morphine compared to those who did not have lower pain scores and opioid requirements in the first 8–24 h postoperatively (Hammer et al. 2005). This suggests that spinal anesthesia with intrathecal morphine may provide effective postoperative analgesia for up to 24 h, which is consistent with known pharmacokinetic profiles of intrathecal morphine. Continuous intrathecal anesthesia and postoperative analgesia has also been used for pediatric cardiac surgery patients. A prospective trial of patients 2 years old or younger, undergoing surgery with CPB randomized patients to preoperative lumbar intrathecal catheter placement dose with bupivacaine intraoperatively and bupivacaine and morphine infusion postoperatively compared to IV opioid therapy showed significantly reduced stress hormone levels including epinephrine and norepinephrine as well as lower lactate levels at the expense of higher fluid requirements. This suggests that continuous spinal anesthesia and analgesia may attenuate the stress response to cardiac surgery and CPB in infants and children; however, other clinical outcomes, including the effect on morbidity was not specifically investigated (Humphreys et al. 2005).

Risks of Neuraxial Techniques in Cardiac Surgery

There is a wide variety in the estimates of the incidence of epidural hematoma ranging from 13 in 850,000 epidural and 7 in 650,000 spinal approaches in patients without anticoagulation (Caruso et al. 2019) to 1 in 1500 to 1 in 68,000 in cardiac surgery patients (Landoni et al. 2015). A prospective audit from 2005 of TEA in adult cardiac surgical cases spanning 13 years and over 2000 patients at a single institution revealed no permanent neurological deficits, with complications of dural puncture in 0.85% and temporary neurological deficits in the form of monoplegia in 0.18% (Chakravarthy et al. 2005). A later review of the literature from 2012 assessing the risk of epidural catheterization in cardiac surgery in adults and children identified 3 cases or 1 in 5493 cases reviewed of serious epidural hematoma requiring urgent surgical intervention, with multiple cases of permanent neurological deficits (Hemmerling et al. 2013). A more recent review of the literature from 2015 identified nine published cases of epidural hematomas and reports of 16 additional nonpublished hematomas, with a

calculated risk of 1 in 3552 cases of TEA in cardiac surgery (Landoni et al. 2015). When neuraxial techniques are used for cardiac surgery, it is generally wise to take the following precautions: ensure normal coagulation parameters before placement and removal of the catheter, avoid repeated attempts, if traumatic puncture, consider delaying surgery requiring systemic heparinization for 214 h, wait 1 h after neuraxial technique prior to heparinization, and ensure vigilant neurological monitoring postoperatively, and considering urgent surgical decompression within 8 h if evidence of hematoma causing neurological deficit (Devarajan et al. 2021; Hemmerling et al. 2013). Although other regional anesthesia techniques, including paraspinal and chest wall blocks, have less risk of neurological damage from an epidural hematoma and may be considered in patients with contraindications to neuraxial techniques (Tsui et al. 2019a), the American Society of Regional Anesthesia and Pain Medicine still recommends following guidelines for neuraxial techniques in patients taking anticoagulant or antiplatelet medications for deep blocks, with specific risk and benefit considerations in more superficial blocks including vascularity, compressibility, and consequences of bleeding (Horlocker et al. 2018).

Paraspinal Regional Anesthesia Techniques

Paravertebral Block

Paravertebral block can have great utility in providing analgesia in a variety of surgical procedures involving the thorax and chest wall, as it can provide unilateral or bilateral segmental visceral and somatic nociceptive blockade. The paravertebral space is bordered posteromedially by the vertebral column, anterolaterally by the parietal pleura, and posteriorly by the costotransverse ligament, and is therefore continuous with the epidural space medially and intercostal space laterally (Fig. 3). It contains the thoracic spinal nerves as they exit the vertebral column as well

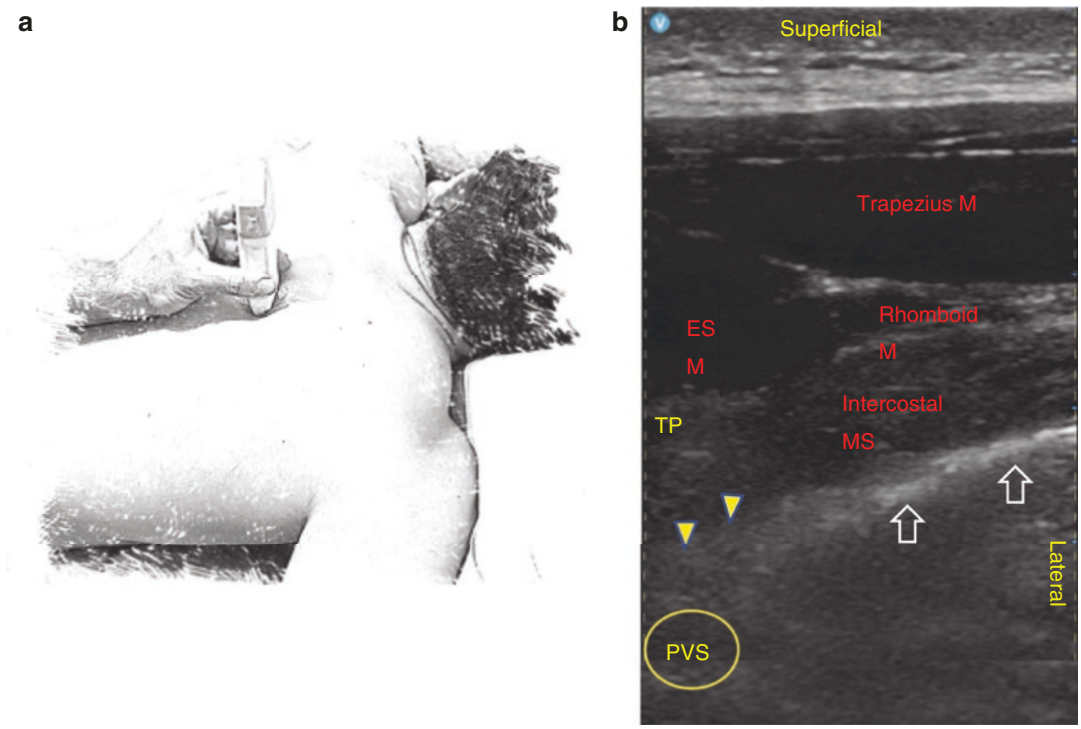

Fig. 3 Ultrasound-guided Paravertebral Block (PVB). (**a**) Position of the ultrasound probe to achieve the transverse approach to the paravertebral space (PVS). Blue dot is the location of the needle approach. (**b**) Ultrasonographic image of PVS. PVS is located ventral to superior costotransverse ligament (small yellow arrows) and posterior to transverse process (TP). White hollow arrows show the pleura. *ESM* erector spinae muscle

as the sympathetic chain, and local anesthetics in the paravertebral space may spread multiple levels cephalad and caudad to cover multiple segmental levels (Karmakar 2001). Although PVB has a potentially lower risk for serious complications, including hematoma causing compression of neuraxial structures and dural puncture, the same basic risks and often contraindications to neuraxial anesthesia/analgesia applies. Paravertebral blocks provide a desirable option for certain cardiac surgeries, including those performed via thoracotomy, given the unilateral nature of the block with effective analgesia and fewer side effects than TEA (Devarajan et al. 2021). Multiple systematic reviews have suggested that continuous PVB may be as effective as TEA for post-thoracotomy pain with lower incidence of adverse effects including hypotension (likely related to unilateral sympathetic blockade with unilateral PVB), urinary retention, and nausea and vomiting (Davies et al. 2006; Ding et al. 2014; Yeung et al. 2016; Scarfe et al. 2016). Bilateral paravertebral blocks have also been used as an alternative to TEA in cardiac surgery requiring median sternotomy, with a retrospective propensity-matched study of 121 patients who received PVB matched to similar patients who received general anesthesia only showing evidence of higher rates of extubation in the operating room, shorter time to extubation, and less opioid consumption (Naganuma et al. 2021). Paravertebral blocks may also be useful for minimally invasive cardiac surgeries. Compared to no block, multi-level single shot PVB for totally endoscopic robotic mitral valve repair leads to higher patient satisfaction postoperatively, with decreased pain and opioid consumption in the first 4 h postoperatively (Neuburger et al. 2015). There is also evidence that analgesia from continuous PVB may be equivalent to TEA for minimally invasive cardiac surgery. A randomized trial of 36 patients undergoing minimally invasive robot-assisted CABG showed no difference in pain scores, opioid consumption, or hemodynamic or respiratory parameters postoperatively in patients who received TEA versus continuous unilateral PVB (Mehta et al. 2008). A similar study comparing TEA to continuous unilateral PVB for patients undergoing minithoracotomy for minimally invasive direct coronary artery bypass again showed no difference in pain scores at rest or coughing postoperatively, with the only significant difference being higher cardiac index with TEA at four and 6 h postoperatively (Dhole et al. 2001). Although the same considerations for patients receiving anticoagulant or antiplatelet therapies for neuraxial procedures are recommended for paravertebral blocks, the risk of PVB and paravertebral epidural hematomas in cardiac surgery patients is unknown. To date, there are no published reports of neurological damage related to PVB in cardiac surgery.

PVBs have also been successfully used in pediatric cardiac surgery patients, although the data is much more limited. One retrospective review of pediatric patients who received single-shot unilateral or bilateral PVB for fast-track cardiac surgery showed shorter time to extubation, lower opioid requirements, and pain scores, shorter ICU LOS compared to historical controls (Sahajanandan et al. 2021). Overall the data suggest that PVB is a valuable tool for analgesia for cardiac surgery, especially for thoracotomy and minimally invasive approaches, and may be safe and effective in pediatric patients as well; however, more studies are needed to investigate their use in this population.

Erector Spinae Plane Block

As the chest wall is mainly innervated by the thoracic spinal nerves, targeting these nerves at their origin, such as with neuraxial or paravertebral techniques, may provide more complete analgesia than targeting nerves at more distal points after branches have already departed. The erector spinae plane (ESP) block provides a potential way to target both dorsal and ventral rami of the spinal nerves and potentially visceral/sympathetic blockade as well, and is technically easier and confers less risk than the neuraxial and paravertebral blocks. The erector spinae muscles run longitudinally on either side of the spine, superficial to the transverse processes. Injection of local anesthetics in the plane between the transverse process and erector spinae muscles (Fig. 4) may

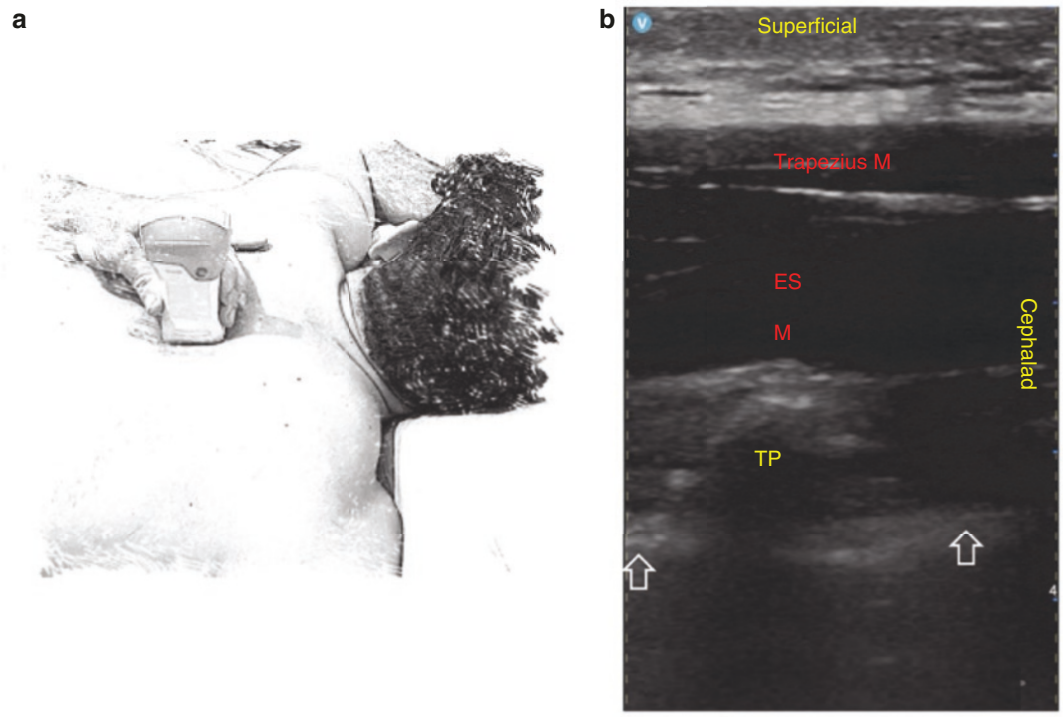

Fig. 4 Ultrasound-guided Erector Spine Plane (ESP) block. (**a**) Position of the ultrasound probe for the thoracic ESP block. Blue dot is the location of the needle approach. (**b**) Erector spinae muscle (ESM) located dorsal to the transverse process (TP). White hollow arrows show the pleura

spread three to eight levels, blocking the dorsal rami as they traverse this plane, and may also spread into the paravertebral space causing blockade of the ventral rami and potentially some visceral nociceptive/sympathetic blockade as well (Helander et al. 2019; Chin et al. 2019; Forero et al. 2016; Diwan et al. 2019; Forero et al. 2017; Tsui et al. 2019b). A case report from 2018 described bilateral ESP catheters with intermittent bolus dosing postoperatively in a patient who had undergone sternotomy with CPB for anomalous right coronary artery reimplantation (Tsui et al. 2018). Subsequently, a pilot study of patients undergoing cardiac surgery randomized 50 patients to receive TEA or ESP catheters the day before surgery with both groups dosed with bupivacaine and continued on infusions for 48 h after extubation, with results showing comparable pain scores postoperatively with all patients having scores less than 4, and no difference in rescue analgesics, intraoperative opioids, or ventilator duration, suggesting that continuous ESP block may be an effective alternative to TEA for analgesia after sternotomy (Nagaraja et al. 2018). A retrospective of 47 patients undergoing fast-track cardiac surgery who received continuous ESP blocks prior to incision and continued up to 72 h matched with similar historical controls showed evidence of decreased opioid requirements in the first 48 h, earlier mobilization, and earlier removal of chest drains as well as decreased hypotension and nausea and vomiting compared to controls. Although this data is retrospective and matched to historical controls, it suggests that incorporating ESP blocks with continuous catheters as part of a fast-track pathway may benefit reducing opioid consumption and earlier mobilization after cardiac surgery (Macaire et al. 2019). More recently, a prospective study randomized patients undergoing cardiac surgery with CPB to ESP block versus acetaminophen and tramadol postoperatively

showed lower pain scores for up to 12 h after extubation, longer time to rescue analgesia and lower overall rescue analgesia requirements, less intraoperative opioid use, and shorter time to extubation in the group that received ESP blocks. This confirms that ESP block provides analgesia in the immediate postoperative period for sternotomy; however, its efficacy and duration as well as impacts on clinical outcomes compared to other regional techniques, is not clear (Krishna et al. 2019). There is even a case report describing an opioid-free anesthetic for a 74-year-old patient undergoing CABG who had bilateral ESP blocks with catheters placed preoperatively was treated with multimodal analgesia including dexmedetomidine, ketamine, and magnesium intraoperatively, continued on ESP ropivacaine infusion plus extra demand doses through postoperative day two and received only one dose of oral opioids postoperatively prior to discharge (Chanowski et al. 2019).

ESP blocks have also been increasingly utilized in pediatric cardiac surgery patients as well. An initial case report from 2018 described a 17-year-old patient who suffered cardiac arrest and ventricular arrhythmia with a complete myocardial bridge and stress-induced ischemia who underwent sternotomy for resection of the myocardial bridge and concomitant defibrillator implant, with the placement of bilateral ESP catheters with an intermittent bolus of ropivacaine postoperatively through postoperative day three. The patient also had hydromorphone PCA immediately after surgery, had pain scores of 0 in the first 24 h, and was managed with low-dose oxycodone thereafter, with the catheters removed on a postoperative day three with the removal of the mediastinal drains (Wong et al. 2018). More recently, a prospective study of pediatric patients undergoing cardiac surgery with midline sternotomy randomized to either bilateral single-shot ESP block versus standard of care showed lower pain scores up to 10 h postoperatively, reduced postoperative opioid consumption, sedation scores, and ICU LOS, suggesting that ESP block can reduce postoperative pain immediately after surgery and may have other beneficial effects (Kaushal et al. 2020).

Chest Wall Blocks

Given that the intercostal nerves provide most of the innervation to the chest, specifically targeting these nerves can have many applications depending on the surgical approach. There are many different sites that these nerves have been targeted for cardiac surgery beyond the neuraxial and paraspinal approaches. Fascial plane blocks offer advantages of being technically easy to perform under ultrasound guidance with relatively safe adverse effect profiles and may offer reasonable alternatives when neuraxial approaches are not possible. Although the data on the utility of chest wall blocks for cardiac surgery are limited, it is an expanding field with a growing body of evidence and will likely only continue to be investigated for acute perioperative pain management in adult and pediatric cardiac surgery.

Continuous Wound Infiltration and Intraoperative Parasternal Intercostal Blocks

Although continuous wound infiltration of local anesthetics intraoperative surgeon-administered parasternal blocks are not specific regional anesthesia techniques, they are technically simple and commonly performed for cardiac surgery and may provide some analgesic benefit without significant risk of bleeding (Nachiyunde and Lam 2018). Although a small randomized study of parasternal intercostal blocks failed to show any difference in pain scores or outcomes other than reduced opioid consumption in the first 4 hours postoperatively (McDonald et al. 2005), a subsequent prospective trial of adult patients randomized to bilateral parasternal intercostal blocks with ropivacaine versus saline prior to sternal closure showed benefits of lower pain scores at the time of extubation and reduced opioid consumption in the first 24 h (Barr et al. 2007). However, two separate prospective randomized trials of continuous wound infiltration of long-acting local anesthetics in pediatric cardiac surgery patients showed evidence of less opioid consumption in only patients weighing greater than 6.3 kg in one study, and no difference in opi-

oid consumption or other measured outcomes in the other (Mattila et al. 2016; Tirotta et al. 2009). There have been some beneficial results in children as well, with one prospective trial of children undergoing cardiac surgery with median sternotomy randomized patients to receive parasternal intercostal ropivacaine versus saline prior to sternal closure, with evidence of shorter time to extubation, less opioid consumption in 24 h, and lower pain scores at multiple time points up to 20 h, suggesting that these blocks can have postoperative benefits for pediatric patients (Chaudhary et al. 2012). Liposomal bupivacaine, a formulation of local anesthetic with extended-release and duration of action for up to 72 h approved for local infiltration and interscalene brachial plexus blocks, has also been of interest in various regional anesthesia and local infiltration applications, including in cardiac surgery. However, a randomized trial of liposomal bupivacaine versus placebo for surgeon-administered parasternal intercostal nerve blocks failed to find any difference in pain scores or postoperative opioid requirements (Lee et al. 2019).

Parasternal Intercostal Plane Block

The parasternal intercostal plane (PIP) blocks encompass various procedures described in the literature (El-Boghdadly et al. 2021). The superficial PIP block targets the plane superficial to the internal intercostal muscles and ribs and deep to the pectoralis major muscle lateral to the sternum (Fig. 5) and has also been described as parasternal intercostal plane block, pectointercostal fas-

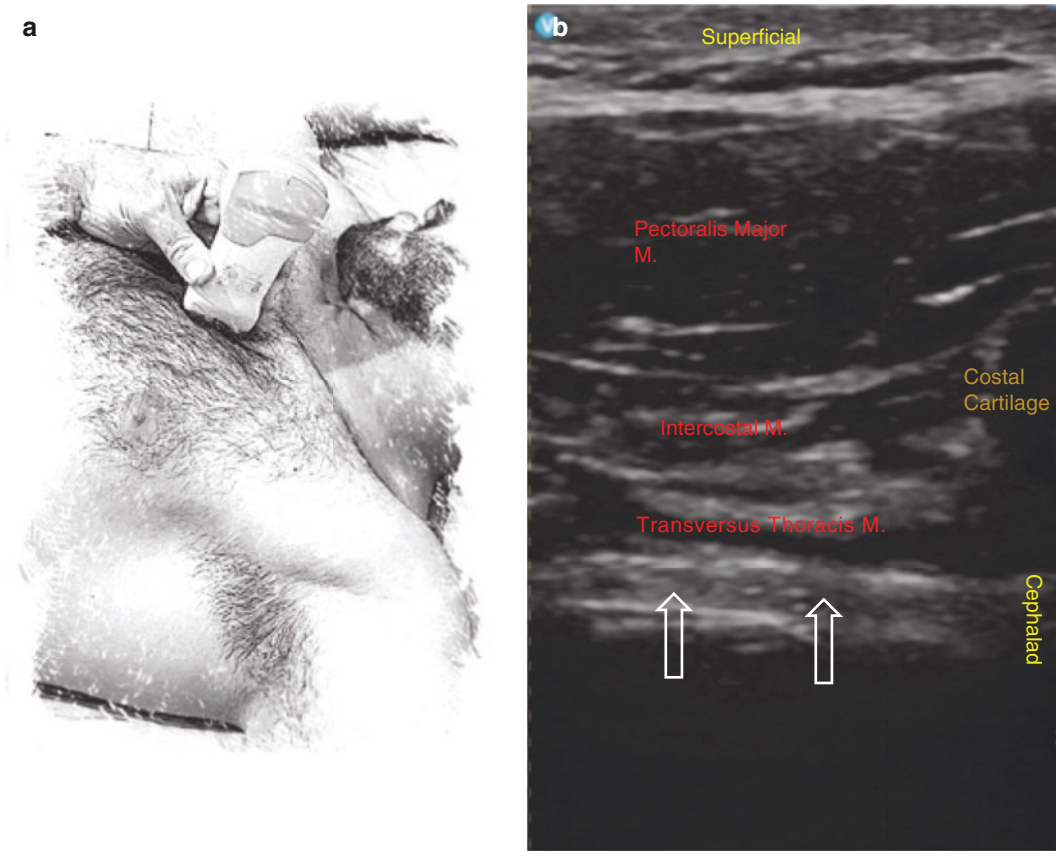

Fig. 5 Ultrasound-guided Parasternal Intercostal Plane block. (**a**) Position of the probe for the PIP Blocks. Blue dot is the location of the needle approach. (**b**) Ultrasound image of PIP. Superficial PIP is the fascia plane between pectoralis major and intercostal muscles. The deep PIP is the fascia plane between intercostal and transversus thoracis muscles. White hollow arrows show the pleura

cial plane block, subpectoral interfascial plane block, and parasternal pecs block in the literature. The deep PIP block targets the plane between the internal intercostal muscle and transversus thoracis muscles and has also been known as the transversus thoracis muscle plane block. The superficial and deep PIP blocks aim to block the anterior cutaneous branches off intercostal nerves two through six, providing sensory innervation to the anterior chest wall and sternum. Potential risks including bleeding with close relation to the internal thoracic vessels with latent altered anatomy if prior vessel/conduit dissection, as well as pneumothorax (Fujii et al. 2019a). Initial case reports of the deep PIP block from 2015 described its use in combination with pectoserratus block for breast surgery (Ueshima and Kitamura 2015), as well as a cadaveric study demonstrating the spread of dye in the fascial plane from a single injection covering intercostal spaces two through five (Ueshima et al. 2015). Subsequent case reports described the placement of deep PIP catheters with intermittent bolus dosing for 2 days after sternotomy for patients undergoing aortic valve replacement and thymectomy with good effect (Ueshima and Otake 2017). Superficial PIP blocks have also successfully been used as a rescue technique for severe postoperative pain after sternotomy that causing hemodynamic instability, providing almost immediate pain relief and good analgesia for over 12 h (Liu et al. 2018). Since these initial case reports, there has been increased interest in this block for pain related to sternotomy. A small pilot study of deep PIP block for sternotomy showed no evidence of block-related adverse events (Fujii et al. 2019b). More recently, a prospective trial of adults undergoing cardiac surgery with sternotomy randomized patients to deep PIP block versus sham block, with results showing reduced static and dynamic pain scores up to 12 h, reduced opioid consumption in 24 h, and less opioid-related adverse effects including nausea and vomiting and pruritis (Aydin et al. 2020). This study suggests that deep PIP block may be have benefits including reducing opioid consumption in patients undergoing sternotomy. In addition, a prospective trial of adults undergoing sternotomy for CABG randomized patients to superficial PIP versus sham block, with those who received superficial PIP block requiring lower doses of remifentanil to maintain hemodynamic stability, reduced propofol to maintain an adequate and level depth of anesthesia, and reduced inflammatory cytokine levels in the first postoperative week (Bloc et al. 2021). Although the clinical significance of these findings is unclear, the study suggests that preoperative superficial PIP block may have benefits of reduced intraoperative analgesic/anesthetic dosing and attenuate the surgical stress response. Finally, a prospective trial of adults undergoing sternotomy for cardiac surgery randomized to superficial PIP block after sternal closure versus no block showed possible reductions in postoperative opioid requirements and reduced pain scores at 6 and 12 h but not at 0 and 3 h post-op; however, given the small sample size of the study and no data collection beyond 12 h, it is difficult to draw conclusions from this specific study and further larger randomized trials assessing important clinical outcomes are necessary (Kumar et al. 2021).

In addition, deep PIP blocks have been successfully used in pediatric patients undergoing intrathoracic surgery for pectus excavatum repair in combination with serratus anterior plane block (Ueshima and Hiroshi 2017). A recent prospective trial of pediatric patients undergoing median sternotomy for elective cardiac surgery randomized patients to deep PIP block with bupivacaine versus sham block with saline. Patients who received bupivacaine required less opioids and had lower pain scores for 24 h, shorter time to extubation, and shorter ICU LOS, and also had evidence of decreased response to sternotomy and lower intraoperative opioid requirements (Bartlett et al. 2020). These results encourage deep PIP to have multiple benefits both intraoperatively and postoperatively in pediatric patients undergoing sternotomy for cardiac surgery.

Interpectoral Plane and Pectoserratus Plane Block

The interpectoral plane (IPP) and pectoserratus plane (PSP) blocks provide sensory blockade to the upper anterolateral chest wall. The IPP targets

the plane between the pectoralis major and pectoralis minor muscles, blocking the medial and lateral pectoral nerves and perforating branches of the lateral cutaneous branches of the intercostal nerves T2–T6, and is also described as PECS I or superficial pectoralis plane block in the literature (Fig. 6). The PSP targets the plane between the pectoral minor and serratus anterior muscles, blocking branches of the lateral cutaneous branches of intercostal nerves T2–T6 and potentially the long thoracic nerve as well, and is also known as the PECS II or deep pectoralis plane block. Any early report of an IPP block for a cardiac procedure described IPP in addition to intercostal nerve blocks in the first and second intercostal spaces, which provided adequate anesthesia for implantation of a cardiac resynchronization device (Fujiwara et al. 2014). A combination of IPP and PSP was also reported as providing successful rescue analgesia postoperatively in a patient who had to undergo minimally invasive mitral valve repair via a minithoracotomy; on postoperative day one the patient was in respiratory distress, and severe pain, and the IPP and PSP blocks provided rapid analgesia and improved respiratory status which seemed to last for 24 h, and the blocks were actually repeated on postoperative day three for the same indications with repeated good effect (Yalamuri et al. 2017). More recently, several randomized trials have investigated the utility of IPP and PSP blocks in cardiac surgery patients. The combination of bilateral IPP and PSP blocks for adult patients undergoing cardiac surgery with sternotomy was

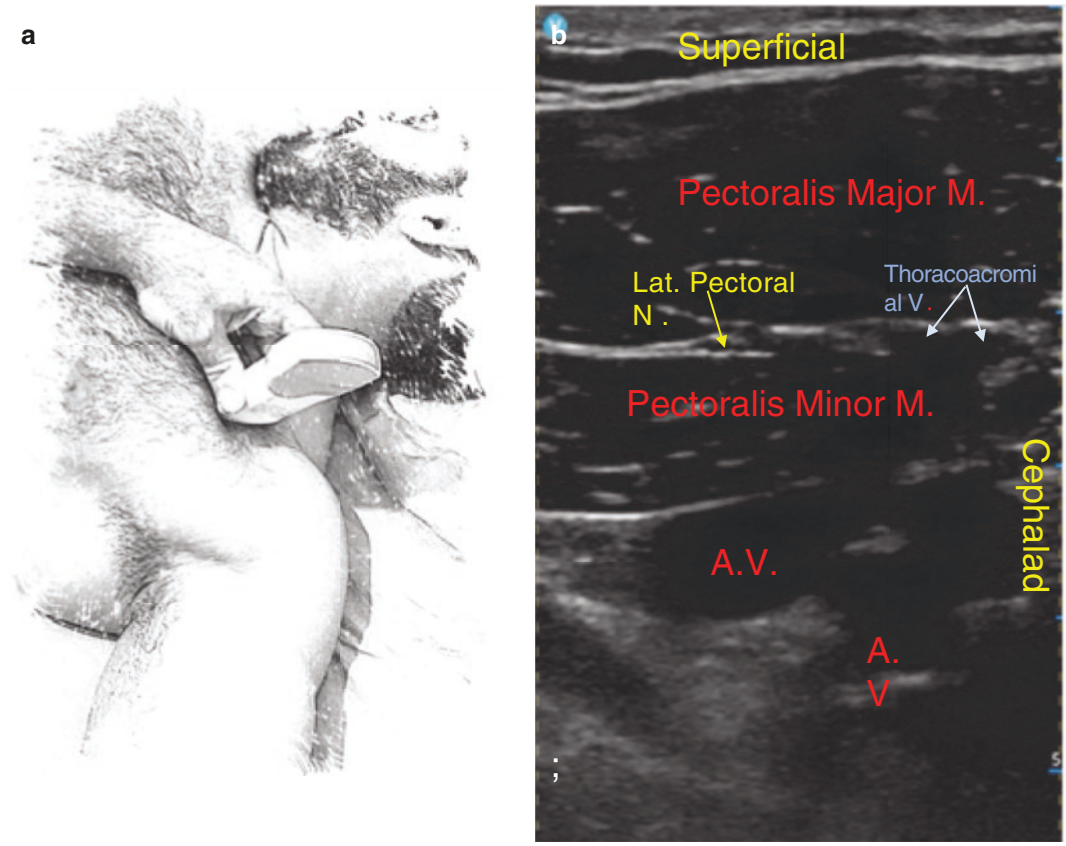

Fig. 6 Ultrasound-guided Interpectoral Plane (IPP) Block. (**a**) Position of the probe for the IPP Block. Blue dot is the location of the needle approach. (**b**) Ultrasound image of IPP. The lateral and medial pectoral nerves along with thoracoacromial vessels run between pectoralis major and pectoralis minor muscles. Axillary artery (A.A.), axillary vein (A.V.)

compared to no block, with patients who received blocks demonstrating lower pain scores up to 18 h as well as shorter mechanical ventilation time and improved peak flow measurements (Kumar et al. 2018). However, a later study of patients undergoing cardiac surgery with sternotomy randomized 80 patients to receive either PSP block versus sham block and although pain scores were initially lower, there was no difference in opioid requirements in the first 48 h or other significant differences between the groups (Khera et al. 2021). There is no real data on the use of IPP or PSP blocks in pediatric surgery patients currently, and more studies are needed to further investigate if they are beneficial in adult cardiac surgery patients as well.

Serratus Anterior Plane Block

The lateral cutaneous branches of the intercostal nerves traverse through the serratus anterior muscle and innervate much of the lateral chest wall. The serratus anterior muscle originates on ribs one through 8 and inserts on the scapula, and injection of local anesthetic in the fascial plane, either superficial to or deep to the muscle itself, can provide effective analgesia of the chest wall in the T2–T9 distribution (Fig. 7) (Helander et al. 2019; Biswas et al. 2018; Blanco et al. 2013). The block is commonly performed under ultrasound guidance in the lateral decubitus or supine position, with the advancement of the needle in the midaxillary or posterior axillary line at the level of the fourth or fifth rib, penetrating the latissimus dorsi muscle posteriorly or the pectoralis muscles anterior before approaching the serratus anterior muscle overlying the rib. Potential complications include pneumothorax and winged scapula from blockade of the long thoracic nerve. Multiple systematic reviews of SAPB in thoracic surgery, including video-assisted and thoracotomy approaches, suggested that the block may help reduce pain scores and opioid consumption, in

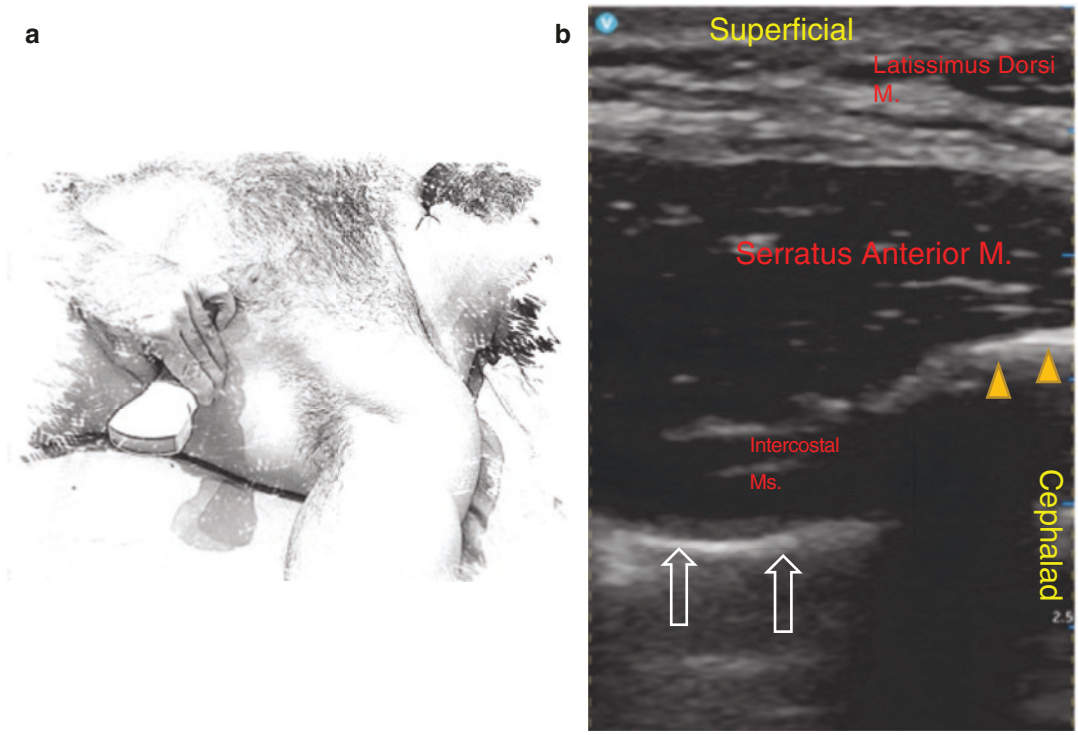

Fig. 7 Ultrasound-guided Serratus Anterior Plane (SAP) block. (**a**) Position of the probe for the SAP block. Blue dot is the location of the needle approach. (**b**) Ultrasound image of SAP. Interfascial injection is usually performed between latissimus dorsi muscle and serratus anterior muscle or between serratus anterior muscle and intercostal muscle. White hollow arrows show the pleura. Solid yellow arrows show the rib

some cases up to 24 h, with many studies showing a shorter effect time of 6–12 h, and subgroup analysis failing to find a significant effect for thoracotomy (Liu et al. 2020; Jack et al. 2020). To date, there has been one observational cohort study investigating the utility of continuous SAP block for adult patients undergoing mitral valve surgery via minithoracotomy. In this study, patients were treated with either preoperative single-shot SAPB and post-closure insertion of SAP catheter with postoperative ropivacaine infusion for 48 h versus IV opioids at the anesthesiologist's discretion. A post-hoc analysis showed no difference in pain at 24 h but significantly less pain at 48 h in patients who were receiving continuous SAP block, as well as less total opioid consumption (Toscano et al. 2020). This preliminary retrospective data suggests that continuous SAP block may be a useful analgesics option for such procedures. In addition to thoracotomy and minithoracotomy procedures, SAP blocks may also be useful for transapical approaches, but future studies will be needed to investigate their efficacy.

In pediatric cardiac surgery, there is limited data on the efficacy of SAP block. One prospective study of pediatric patients undergoing cardiac surgery via thoracotomy randomized patients to receive SAP block, pectoserratus block, or intercostal nerve block prior to surgical incision, with no difference in immediate postoperative pain scores, but reduced pain scores in patients who received in SAP block or PSP block compared to intercostal nerve block between 6–10 h and 6–10 h, respectively. Also, both SAP and PSP block patients had lower opioid requirements postoperatively compared to intercostal nerve blocks, but no difference in time to extubation or adverse effects (Kaushal et al. 2019). This limited data suggests that SAP and PSP blocks may be effective options for analgesia and have a longer duration than intercostal nerve blocks for pediatric patients undergoing cardiac surgery via thoracotomy.

Conclusions and Future Directions

Adequate perioperative pain control for adult and pediatric cardiac surgery patients is essential to ensure optimal patient outcomes and prevent complications associated with pain and its related stress response and respiratory complications. The field has been shifting from relying mostly on high-dose opioid therapy to multimodal analgesia and regional anesthesia. The rapid expansion of chest wall blocks which may provide technically easier approaches with less risk than neuraxial approaches provides new opportunities for investigating the optimal analgesia approach after cardiac surgery. To date, there is very limited data on the optimal analgesic approach for these patient populations, especially with regard to pediatric patients. Future studies with larger sample sizes addressing the impacts of these techniques on important clinical outcomes, including morbidity in addition to pain and opioid consumption, will be important. Additionally, further head-to-head comparisons of various regional anesthesia techniques will be needed to determine which may provide optimal analgesia.

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Chronic Postoperative Pain in Congenital Heart Disease Patients

Jenny Zhao Cheng and Michael G. Fitzsimons

Abstract

Chronic pain is a potential sequela of any surgical procedures. Children and adolescents with congenital heart disease may develop chronic postsurgical pain syndrome that persists into the years of critical social, emotional, and physical development. Adults with congenital heart disease may have suffered from years of chronic pain. Chronic pain after cardiac surgical procedures for congenital heart disease is less well studied than procedures for acquired conditions. Assessment of chronic postsurgical pain is complicated in the pediatric population as language development may be incomplete at a particular age or may have been impacted by complications of congenital heart disease. Effective preventative techniques for the prevention of chronic pain have not been clearly identified in this population. Effective treatment of chronic postsurgical pain often requires a multimodal approach and includes pharmacological management, interventional procedures, psychotherapy, and other modalities. This chapter will explore definitions of chronic postsurgical pain, incidence and risk factors, mechanisms of chronic pain, management, and prognosis.

Keywords

Congenital heart disease · Chronic pain · Chronic postsurgical pain · Cardiac surgery · Pain management · Opioids · Pain

Introduction

Chronic postoperative pain is a potential sequela of any surgical procedure. Chronic postoperative pain in patients with congenital heart disease impacts two populations, children who have undergone procedures early in life and adults who undergo procedures or have lived with congenital heart disease for many years. Pediatric and adolescent patients may have pain syndromes that persist into the years of physical and social development while adults with congenital heart disease may have experienced years of pain or may develop a chronic pain syndrome after a surgical procedure later in life. Most studies of chronic pain after cardiac procedures are performed in adult patients that have undergone more common procedures such as coronary

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artery bypass grafting (CABG) or valve interventions making generalization to the congenital heart disease population difficult. This is less of an issue in the pediatric patient whose procedures are largely related to congenital cardiac conditions. This chapter addresses definitions of chronic postsurgical pain (CPSP) in children and adult patients with congenital heart disease, the incidence and risk factors, impact, mechanisms of chronic postsurgical pain, preventative efforts, and modes of management.

Definition of Chronic Postsurgical Pain

The development of persistent pain after cardiac surgery for congenital heart disease is an unexpected but common complication. Multiple names and definitions have been suggested including "Chronic postsurgical pain (CPSP)" or "Persistent postsurgical pain (PPSP)" (Macrae and Davies 1999). Macrae and Davies then defined CPSP as pain that develops after a surgical intervention and lasts at least 2 months when other causes have been excluded, including pain from a condition preceding the surgery (Macrae 2001). Werner and Kongsgaard recognized the weaknesses of the definition including the fact that pain was often a factor prior to surgery and that pain is far more complex than discomfort at a specific site. A new definition was suggested: (1) "Pain develops after a surgical procedure or increases in intensity after a surgical procedure"; (2) "Pain should be at least 3–6 months duration and significantly affect the Health-Related Quality of Life (HR-QOL)"; (3) "The pain is a continuation of acute post-surgical pain or develops after an asymptomatic period"; (4) "The pain is either localized to the surgical field, projected to the innervation territory of a nerve situated in the surgical field, or referred to a dermatome (after surgery in deep somatic or visceral tissues)"; and (5) "Other causes of pain should be excluded. i.e. infection or continuing malignancy in cancer surgery" (Werner and Kongsgaard 2014, p. 2, Table 1). This definition is also commonly used in children (Williams et al. 2017).

There is no generally accepted definition for chronic pain after procedures for cardiac conditions in children or adults whether referring to acquired or congenital conditions. Some define the syndrome by the surgical approach including post-sternotomy pain syndrome (PSPS) or chronic post-thoracotomy pain syndrome (CPTPS) (Costa et al. 2015; Koehler and Keenan 2006). Post-CABG pain (PCP) was first defined in adults as "chest wall pain of at least 3 months' duration which first appeared after coronary artery bypass grafting (CABG) or which was different from the preoperative pain (angina pectoris), in case it was present prior to the operation" by a retrospective cohort study in 2001 (Eisenberg et al. 2001, p. 12).

Incidence, Risk Factors, and Impact of Chronic Pain in Patients with Congenital Heart Disease

The incidence, risk factors, and impact of chronic pain in children and young adults with congenital heart disease are not easy to determine. Conditions often lead to surgery and interventional procedures in early life, during adolescence, and later in life through different phases of physical, mental, and social development. Survey questions are not standardized. Time frames may vary. Pain is a subjective measure. Regardless, it appears that surgeons significantly underestimate the incidence of these syndromes (Carle et al. 2009).

Incidence, Risk Factors, and Impact of Chronic Pain in Children and Young Adults with Congenital Heart Disease

Lauridsen et al. studied chronic pain in children after cardiac surgery and defined it as either persistent pain or pain at the site of sternotomy (Lauridsen et al. 2014). More than 1 in 5 (21%) patients reported chronic pain and of those patients, 46% reported pain intensity greater than 4 on a 1–10 pain scale. Among the remaining patients who did not fulfill the criteria for

chronic pain, 20% reported pain at some point provoked by physical activity, pressure at the surgical site, or touching the scar (Lauridsen et al. 2014). Other reports describe an incidence of 17% among children who underwent cardiac surgery (Matsuda et al. 2019; Brou et al. 2019). The rates for chronic post-thoracotomy pain may be lower. Only 3 of 88 adult patients endorsed chronic pain (3.4%) up to 30 years after thoracotomy in childhood (Kristensen et al. 2010). Marchetti et al. reported an incidence of 5.4% (Marchetti et al. 2021). The presence of pain was associated with a lower quality of life (Matsuda et al. 2019).

Identification of risk factors for chronic pain after congenital heart disease surgery could facilitate more focused efforts toward prevention although studies specifically in children are few. Chronic pain is more common after major cardiac surgery compared with more "minor" procedures such as isolated repair of atrial or ventricular septal defects (Lauridsen et al. 2014).

Young adults who had previously been diagnosed and treated for congenital heart disease during infancy or childhood experience post-traumatic stress and illness uncertainty (Moreland and Stantacroce 2018). The difference between congenital heart disease and adult heart disease is the long-term nature of congenital heart disease and the unpredictability of its course and outcome (Mishel 1981). Psychological stress and depressive symptoms can contribute to a lower quality of life and pain scores in these patients (Matsuda et al. 2019). Children with congenital heart disease are more likely to report worse health, missed days of school, and difficulty with crawling, walking, and running, or needing special equipment for such (Razzaghi et al. 2015). Children with congenital heart disease also report higher incidences of attention deficit hyperactivity disorder (ADHD), asthma, and ear infections (Razzaghi et al. 2015). Education about the diagnosis and management of congenital heart disease can be powerful means to help patients cope with the uncertainty of congenital heart disease (Moreland and Stantacroce 2018).

Incidence, Risk Factors, and Impact of Chronic Pain in Adults with Congenital Heart Disease

The incidence of chronic pain after sternotomy in adult patients ranges from 11% to 57% at 1 year after surgery (Gjeilo et al. 2010; Maguire et al. 2006). The large variation is due to differences in presentation and the incidence may still be underestimated (Van Leersum et al. 2010). A systemic review and meta-analysis of pain after cardiac surgery of 23 studies consisting of over 11,000 patients after cardiac surgery revealed an incidence of persistent postoperative pain in 37% in the first 6 months after cardiac surgery and in 17% more than 2 years after the surgery (Guimarães-Pereira et al. 2017).

Risk factors associated with congenital heart disease in adults may be related to the condition, surgical procedure, complexity, or social factors (Table 1). Risk factors associated with development of chronic post-sternotomy pain among adults undergoing general cardiac surgery include the use of internal thoracic artery (ITA) in coronary bypass grafting, history of antidepressant use, hypothyroidism, surgical wound complications, patients on disability benefits, or those scheduled for a consultative medical examination for retirement (Augusto Cray da Costa et al. 2015). A comprehensive 2021 sub-study of the "Assessment of Patterns of Patient-Reported

Table 1 Risk factors for chronic pain in adults with CHD

Major congenital heart disease (i.e., beyond simple ASD or VSD repair)
Female sex
Patients with less than a college degree
Older age at time of surgery
More than one procedure
Surgery or higher complexity
Presence of Eisenmenger syndrome
Need for a surgical conduit
Tricuspid atresia
African American or Non-white Hispanic

ASD atrial septal defect, *CHD* Congenital heart disease, *VSD* ventricular septal defect
Adapted from Apers S, et al. J Cardiol 2015;176:334–342; Leibold A, et al. Int J Cardiol Cong Heart Disease 2021; Kim JH, et al. Pain 2012;158:194–211

Outcomes in Adults with Congenital Heart Disease-International Study" (APPROACH-IS) evaluated the demographic and clinical characteristics associated with chronic pain after congenital heart surgery (Apers et al. 2015; Leibold et al. 2021). Risk factors for chronic pain identified in this study included female sex, individuals with less than a college degree, older age at the time of surgery, individuals undergoing more than one surgery, or surgery of higher complexity (Leibold et al. 2021). The presence of cyanotic heart diseases or Eisenmenger syndrome, and the need for a conduit or tricuspid atresia were also associated with a higher incidence of chronic pain. The prevalence of pain was highest among the groups of patients with cyanotic congenital heart disease or Eisenmenger physiology, conduits, and tricuspid atresia (52.8%, 41.7%, and 41%, respectively) (Leibold et al. 2021). Another analysis revealed that older patients, females, Hispanic, lower educational level, and unmarried status were more likely to report chronic pain (Leibold et al. 2021). Independent risk factors reported by this study included higher disease complexity, cardiac device presence, and the presence of psychiatric or other medical problems (Leibold et al. 2021).

The impact of the persistent chronic pain in adults with congenital heart disease impacts different aspects of life. Most patients with congenital heart disease consider their health to be good (Loup et al. 2009). Those with congenital heart and pain are less likely to report excellent or very good health (Leibold et al. 2021). The presence of chronic pain is also associated with a reported lower quality of life and higher rates of use of tobacco and sedatives but lower rates of alcohol use (Leibold et al. 2021). Higher rates of mental illness are also seen in patients with congenital heart disease who have undergone surgery and suffer from chronic pain (Brou et al. 2019).

Mechanism of Chronic Pain

Multiple mechanisms contribute to the development of chronic postoperative pain after cardiac surgery and other interventional procedures.

The performance of cardiac surgery involves potential injury and direct injury to many tissues via central line placement, patient positioning, skin incision, sternotomy and sternal retraction, separation of muscle, manipulation of visceral tissue, and placement of foreign bodies including sternal wires used for closure and stabilization (Table 2).

Sternotomy and sternal retraction can result in sternal fracture (Moore et al. 1994), brachial plexus injury (Sharma et al. 2000), and first rib fracture (Vander Salm et al. 1980). First rib fracture occurs in 5% of patients (Curtis et al. 1975). Subsequent first rib displacement after fracture may result in injury to the brachial plexus (Vander Salm et al. 1980). Brachial plexus injury occurs in 5% of patients after cardiac surgery and is associated with pain dysesthesias, and hand weakness (Hanson et al. 1983).

Sternal complications associated with healing can also contribute to chronic pain. Incomplete sternal healing results in a higher incidence of chronic pain as well as higher pain intensity (Papadopoulos et al. 2013). Sternal wound infection is associated with an increased incidence of chronic post-sternotomy pain likely due to mediastinitis, keloid formation, and wound dehiscence (Costa et al. 2015). Inflammatory changes associated with wound infection are contributory factors for chronic pain development (Costa et al. 2015).

Table 2 Surgical mechanisms of chronic pain in patients with CHD

Surgical factor	Mechanism of injury and chronic pain
Manipulation and retraction of sternum	Brachial plexus injury
	Sternal fracture
Use of electrocautery	Damage to intercostal nerves
Rib fracture	
First rib fracture	Brachial plexus injury
Emergency surgical procedures	Additional damage to tissue
Surgery associated with repeat sternotomy	Additional tissue damage
Sternal wound infection	Chronic inflammation
	Mediastinitis
	Wound dehiscence

Dissection of the internal thoracic artery can result in intercostal nerve injury (Eng and Wells 1991; Mailis et al. 2000). Patients who have undergone ITA harvest have more chronic pain than patients who have not (Kamalipour et al. 2014).

First and second rib fractures can occur in up to 16% of patients undergoing sternotomy (Woodring et al. 1985). Pain associated with rib fracture may occur in the chest, shoulder, or arm and resemble angina.

Emergent cardiac surgery as well as non-scheduled emergency surgery during the initial hospitalization has been reported as a risk factor for chronic post-sternotomy pain (van Gulik et al. 2011). The reason for this risk is unknown. One hypothesis is that emergent procedures occur under less controlled circumstances and surgical manipulation may be less gentle resulting in more tissue damage.

The transition of acute pain to chronic pain syndromes involves changes in the pain pathway from the level of nociceptive receptors to the brain. Chronic nociceptive pain could occur when an enhanced responsiveness of the nerve fibers develops due to persistent pain or stimulus of heightened intensity. This is referred to as peripheral sensitization (Scholz 2014). Peripheral sensitization results in "increased action potential firing and transmitter release in the dorsal horn of the spinal cord," termed "central sensitization". Neuropathic pain occurs when injury to peripheral nerves results in changes in the dorsal horn of the spinal cord such that central sensitization occurs as well as a reduction in the inhibitory input through pathways from the brainstem.

Assessment of Chronic Pain in Patients with Congenital Heart Disease

Comprehensive assessment of patients with congenital heart disease presenting with chronic pain involves a multidimensional approach regardless of whether presentation occurs during childhood or the adult years.

Pain assessment in children differs from adults due to the subjective nature of pain, limited language development in children, dependence upon others, as well as differences in the expression of pain based upon factors such as sex or ethnicity (Manworren and Stinson 2016). Parents and guardians of children are encouraged to support their children in the assessment of the children's pain experience.

Comprehensive pain assessment begins with inquiry into the heart condition, prior surgical and interventional procedures, as well as investigation into any preexisting chronic pain syndromes not associated with the congenital condition. Pain assessment in children and adults should include: (1) intensity of pain; (2) location of pain as well as radiation to other locations; (3) duration of pain; (4) sensory qualities using word descriptors (e.g., stabbing, dull, aching); (5) cognitive aspects of pain (impact on daily activities or quality of life); (6) affective aspects such as unpleasantness of pain; and (7) any factors that may affect the patient's perception of pain (Manworren and Stinson 2016). Other assessments include whether patient has an exaggerated response to painful stimuli (hyperalgesia) or whether pain occurs when stimuli that are normally not painful occur (allodynia) (Scholz 2014). Chronic pain may also manifest as heightened sensitivity to heat (thermal hyperalgesia) or decreased sensitivity to stimulation (hypoesthesia) (Courtney et al. 2017). Pain assessment should be accompanied by additional interviews and assessments for social, emotional, cognitive, environmental, and behavioral aspects of patient's chronic pain (Dansie and Turk 2013).

Assessment of pain in children should not only describe the quantification of pain intensity, but also the significance and context of the pain experience of the pediatric patient (Johnston 1998).

Numerous assessment tools are available to assess acute and chronic pain in children and adolescents. Developmentally appropriate pain assessment tools include Adolescent Pediatric Pain Tool (APPT), Bath Adolescent Pain Questionnaire (BAPQ), Faces Pain Scale-Revised (FPS-R), Numeric Rating Scale (NRS), Vouchers,

Pediatric Pain Assessment Tool (PPAT), Pediatric Pain Questionnaire (PPQ), Visual Analog Scale (VAS), and Wong-Baker Faces Pain Rating Scale (WBPRS).

The VAS is a simple method used by patients eight years of age or older. The patient marks their pain intensity across a 10 cm line (Scott and Huskisson 1979). The WBPRS is another widely used pain scale that displays a series of six faces, from a happy face at 0 ("no hurt") to a crying face at 10 ("hurts worst"), and asks the patient to choose the face that best describes the intensity of their pain (Wong and Baker 1988). The WBPRS is effective in children as young as three years of age (Wong and Baker 1988). The PPQ is validated for chronic pain assessment and is composed of questions regarding the intensity, location, sensory, evaluative, and affect qualities of pain (Varmi et al. 1987). Pain assessment is not a single action but requires periodic reassessment after an intervention (Manworren and Stinson 2016).

Prevention of Chronic Pain in Congenital Heart Disease

The development of chronic pain is multifactorial including injury associated with initial sternotomy or thoracotomy, secondary injury to structures such as the brachial plexus, inflammation, infection, as well as the emotional components of congenital heart disease in children and adults. The presence of acute pain after sternotomy is a strong risk factor in predicting the presence and intensity of chronic pain (Guimarães-Pereira et al. 2016; Kampe et al. 2017; Choinière et al. 2014; Van Gulik et al. 2011; Carle et al. 2009). Effective treatment of acute pain may reduce the incidence and severity of chronic pain (Kleiman et al. 2017). Pharmacological agents, neuraxial anesthesia, regional anesthesia, surgical techniques, psychotherapy, and other interventions have been studied throughout the perioperative period for effectiveness in treatment of acute pain after cardiac surgery and prevention of long-term chronic pain (Kleiman et al. 2017).

Pharmacologic Intervention

Opioids are the most used medications for interoperative and postsurgical pain, but their use is associated with adverse effects such as addiction and overdose (Dowell et al. 2016). Opioids relieve pain by binding to μ-receptors. Opioids are often more useful treating acute or short-term pain, and less effective in treating chronic pain or improving quality of life in patients with chronic pain because opioid use can lead to opioid tolerance and opioid-induced hyperalgesia (Hayhurst and Durieux 2016). Studies show that only a small portion of patients with chronic post-sternotomy pain received opioids for refractory pain (Beal and Wallace 2016).

Other medications utilized in the perioperative period to manage pain include non-steroidal anti-inflammatory drugs (NSAIDS), acetaminophen, gabapentinoids (gabapentin and pregabalin), ketamine, remifentanil, and dexmedetomidine. NSAIDS, acetaminophen, gabapentinoids, and ketamine all result in reductions in opioid use (Kleiman et al. 2017). Dexmedetomidine reduces acute pain, major adverse cardiac events, and delirium (Ji et al. 2013). Glucocorticoids have been utilized to reduce inflammation. There is no strong evidence that these agents reduce the incidence or intensity of chronic pain after cardiac surgery (Kleiman et al. 2017) (Table 3).

Local Anesthesia, Regional Anesthesia, and Other Interoperative Interventions

Infiltration of local anesthesia, use of regional anesthetic techniques, and other interoperative interventions have been utilized to reduce acute pain and potentially reduce the development of chronic pain (Kleiman et al. 2017) (Table 4). Reductions in acute pain are reported with thoracic epidural anesthesia, intrathecal opioids, parasternal or paravertebral blocks, and continuous catheter-based infusions of local anesthetics but none of these techniques have been shown to consistently reduce the incidence of chronic pain. Delivery of local anesthesia via a continuous

Table 3 Pharmacologic post-sternotomy/thoracotomy pain prevention measures and impact on chronic pain

Intervention	Mechanism and acute effects	Effect on chronic pain
NSAIDS	Non-selective inhibition of cyclooxygenase (COX) enzymes including COX-1 and COX-2; use of diclofenac resulted in a reduction in use of morphine after cardiac surgery	No strong data indicating a reduction in chronic pain
Acetaminophen	Inhibition of prostaglandin synthesis; studies generally show a reduction in opioid use in first 24 h after cardiac surgery	No strong data indicating reduction in chronic post-sternotomy pain
Gabapentinoids	GABA analogue that binds to voltage-gated calcium channels; reduces acute pain after cardiac surgery and opioid use	Perioperative use of both gabapentin and pregabalin *reduces* incidence of chronic pain
Ketamine	Interactions with opioid receptors, monoaminergic receptors, muscarinic receptors, voltage-sensitive calcium channels, and NMDA antagonist action; reduction in acute use of opioids, reduces inflammation, and improves patient satisfaction	No studies in chronic post-sternotomy patients
Remifentanil	Rapid acting μ-opioid receptor agonist metabolized by blood and tissue esterases	Perioperative use results in tachyphylaxis, opioid induces hyperalgesia, and *increased* incidence of chronic pain
Dexmedetomidine	Selective α-2 agonist primarily used for sedation; use results in a decrease in acute postoperative pain, major adverse cardiac events, and delirium	No strong evidence of a reduction in incidence of chronic pain
Glucocorticoids	Inhibition of inflammatory processes	No evidence of a reduction in chronic pain

GABA GAMMA-aminobutyric acid, *NMDA N*-methyl-D-aspartic acid, NSAIDS non-steroidal anti-inflammatory drugs
Adapted from Kleiman et al, Regional Anesthesia and Pain Medicine 2017;42:698–708

Table 4 Local, regional, and interventional techniques to reduce pain after cardiac surgery and impact on chronic pain

Intervention	Mechanism and acute effects	Effect on chronic pain
Application of transdermal lidocaine	Application of a patch of local anesthetic to site of surgical incision	No evidence to support use to reduce chronic pain
Thoracic epidural anesthesia	Direct application of local anesthetic to nerve roots within spinal column; results in reduction in pain scores and cardiopulmonary complications	No evidence to support use to reduce chronic pain
Intrathecal opioids	Intrathecal injection of morphine prior to cardiac surgery; improved analgesia and reduction in morphine use	No strong evidence to support use to reduce chronic pain
Parasternal intercostal and paravertebral blocks	Regional application of local anesthetic to thoracic intercostal nerves; technique results in a reduction in acute pain	No evidence of a reduction in chronic pain
Continuous wound catheter	Continuous infusion of local anesthetic; technique results in a significant reduction in acute postoperative pain and a potential reduction in length of stay; complications such as tissue necrosis, wound infection, and cellulitis have been reported	No evidence of a reduction in chronic pain

Adapted from Kleiman et al, Regional Anesthesia and Pain Medicine 2017;42:698–708

wound catheter has resulted in cellulitis, necrosis, and surgical wound infections (Brown and Morrison 2004). Osteopathic manipulative treatment has been used successfully in patients with post-sternotomy pain (Bordoni et al. 2017). Acupuncture and trigger point injection have been used successfully in post-sternotomy pain syndrome (Allam 2020).

Treatment of Chronic Pain Associated with Congenital Heart Disease

Management of chronic postoperative pain in patients with congenital heart disease includes pharmacological management, interventional procedures, psychotherapy, and other modalities (Kleiman et al. 2017).

Reversible causes of contributors to chronic pain must be ruled out. Radiographic imaging is a critical component of assessment. Imaging modalities include chest X-ray, multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), and scintigraphy (Hota et al. 2018). Pain may be due to hardware complications, osseous complications, or infectious complications (Table 5) (Hota et al. 2018).

If such factors are not found, then a conservative approach may include the use of agents effective for neuropathic pain including gabapentinoids, selective serotonin reuptake inhibitors (SSRIs), or tricyclic antidepressants (Guimarães-Pereira et al. 2017; Bates et al. 2019).

The use of opioids for treatment of chronic pain should be considered very carefully. Nearly 10% of patients who are opioid naïve going into cardiac surgery are utilizing opioids over 90 days afterward (Brown et al. 2020).

Interventional procedures and adjunct options are an option for patients who do not respond to conservative management. Procedures and adjunct options include placement of a spinal cord stimulator, radiofrequency ablation, and transcutaneous electrical nerve stimulation (TENS) (Table 6).

Table 5 Potential causes of post-sternotomy pain on radiographic imaging

Sternal wire fracture
Sternal wire migration
Sternal deshiscence
Sternal non-union
Osseous or cartilaginous fracture
Hematoma
Mediastinitis
Deep sternal abscess
Sternal osteomyelitis

Adapted from Hota et al, AJR 2018;211:1194–1205

Table 6 Adjunct techniques to reduce pain after cardiac surgery and impact on chronic pain

Intervention	Mechanism and acute effects	Effect on chronic pain
Transcutaneous electrical nerve stimulation (TENS)	Use of TENS was more effective than placebo; reduces opioid and non-opioid medication use following cardiac surgery	Mixed results
Sternal wire removal	Sternal wires removed in patients with chronic pain, potentially attributed to wires; other causes of pain such as infection, myocardial ischemia, or costosternal instability should be eliminated	Wire removal results in a high incidence of reduction in cessation of chronic pain
Psychological interventions		Telephone-derived collaborative care for patients with depression results in improved pain scores up to one year after cardiac surgery
Osteopathic manipulative therapy	Release fascial restrictions, mobilize tight ligaments, and drain congested lymphatic channels	Reduction in chronic post-sternotomy pain (case report)

Adapted from Kleiman et al, Regional Anesthesia and Pain Medicine 2017;42:698–708

Spinal Cord Stimulation

Spinal cord stimulators (SCS) are implanted devices that send low levels of electricity directly into the spinal cord to relieve pain. There is no clear explanation of the mechanism for the observed clinical benefits from the SCS. Spinal cord stimulation has been used to treat angina as well as intractable postoperative neuropathic pain such as chronic thoracic pain (de Leon-Casasola 2009). Spinal cord stimulation has been demonstrated in case reports for children with chronic pain syndromes, but the studies of spinal cold stimulator in children with congenital heart surgeries are lacking (Fan et al. 2020; Kim and Cucchiaro 2017).

Radiofrequency Ablation

Pulsed radiofrequency of dorsal root ganglion is a relatively new neurostimulation modality that aims to address chronic neuropathic pain by stimulating the dorsal root ganglion (Shanthanna et al. 2014). The exact mechanism is unclear but modulation of pain signals to the brain may be the effect (Cahana et al. 2006). Pulsed radiofrequency to the dorsal root ganglia is superior to pharmacotherapy and radiofrequency to the intercostal nerves for patients with chronic postsurgical thoracic pain (Cohen et al. 2006). Studies on its use in congenital heart surgery patients are lacking (de Louw et al. 2002).

Transcutaneous Electrical Nerve Stimulation

Transcutaneous electrical nerve stimulation (TENS) works by the external application of pulsed electrical currents applied to intact skin to "activate underlying nerves" (Johnson 2007). TENS may be self-administered. TENS has been demonstrated to improve acute postoperative analgesia and reduce postoperative opioid requirements in patients undergoing cardiac surgery (Ozturk et al. 2016). TENS has been used for chronic postoperative neuropathic pain in children, but specific studies on its use in congenital heart surgery are lacking (Sittl et al. 2000). More study is needed in patients with chronic pain after cardiac surgery.

Psychotherapy

Psychological factors such as anxiety and depression have been associated with patients' sense of well-being. Patients who have depressive symptoms after cardiac surgery are more likely to report a lower quality of life, have higher pain scores, and ultimately suffer higher mortality compared to patients without depressive symptoms (Connerney et al. 2001; Blumenthal et al. 2003). However, telephone-derived collaborative care for depression after coronary angiography bypass grafting has been demonstrated to reduce pain scores up to one year after surgery (Morone et al. 2010).

Prognosis

Despite all the medication treatments, invasive procedures, and prevention modalities for pain, approximately 50% of patients with chronic postoperative pain still have persistent inadequate relief of pain (Smith et al. 2016). Most studies demonstrated the effectiveness of treatment modalities in the management of acute postoperative pain, but few supported their use in treatment or prevention of chronic post-sternotomy pain. More work must be done in this area, specifically in those patients with congenital heart disease.

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Postoperative Renal Management, Fluid/Electrolyte Management and Acid–Base Disorders

Felice Eugenio Agrò, Marialuisa Vennari, Alessandro Centonze, Giuseppe Pascarella, Piliego Chiara, Carola Sebastiani, and Alessandro Strumia

Abstract

Maintaining electrolyte, acid–base and fluid balance is the final goal of any clinical treatment in the setting of cardiac surgery and in particular with the complex clinic of congenital heart diseases. In these cases, the preservation of fluid, ionic, osmolar and acid–base balance is the sum of complex clinic evaluations and actions, taking into account the kind of surgery, the alterations due to anaesthesia, the effects of cardiopulmonary bypass, patient's comorbidities and his own response to surgical stress. The complexity of clinical management is increased by the strict interconnection existing between electrolytes, acid–base system and fluid distributions: any change in one of them is responsible for modification of both the remainders. Moreover, the balance of each system is physiologically maintained through modification in the balance of the remainders. The character actor of these regulator mechanisms is the kidney: any alteration in renal function modifies the multifaceted homeostasis of the 'milieu intérieur' of the human body. The role played by kidneys is an additional problem in the clinical management of cardiac surgery patients, considering that renal impairment is one of the most frequent complications. In clinical practice, clinicians are often faced with much uncertainty that should be in part overcome through an adequate knowledge of human physiology.

Keywords

Glomerular filtration rate · Renal replacement therapy · Acute kidney injury · Brain natriuretic peptide · Atrial natriuretic peptide

Introduction

Maintaining electrolyte, acid–base and fluid balance is the final goal of any clinical treatment in the setting of cardiac surgery and in particular with the complex clinic of congenital heart diseases (Bignami et al. 2017).

In these cases, the preservation of fluid, ionic, osmolar and acid–base balance is the sum of complex clinic evaluations and actions, taking into account the kind of surgery, the alterations due to anaesthesia, the effects of cardiopulmonary bypass, patient's comorbidities and his own response to surgical stress. The complexity of

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clinical management is increased by the strict interconnection existing between electrolytes, acid–base system and fluid distributions: any change in one of them is responsible for modification of both the remainders. Moreover, the balance of each system is physiologically maintained through modification in the balance of the remainders. The character actor of these regulator mechanisms is the kidney: any alteration in renal function modifies the multifaceted homeostasis of the 'milieu intérieur' of the human body. The role played by kidneys is an additional problem in the clinical management of cardiac surgery patients, considering that renal impairment is one of the most frequent complications (Evans et al. 2018).

In clinical practice, clinicians are often faced with much uncertainty that should be in part overcome through an adequate knowledge of human physiology.

Physiology: From Birth to Adults

Fluid Balance and Distribution

In adults, the total body water (TBW) represents the 60% of the body weight. It is mainly distributed in the intracellular space (ICS = 55% of body water) and the extracellular space (ECS = 45%). The ECS is divided into three additional compartments:

- The intravascular space (IVS, plasma = 15% of ECS)
- The interstitial space (ISS = 45% of ECS)
- The transcellular space (TCS = 40% of ECS) (Agrò and Vennari 2013) (Fig. 1)

The TCS is a functional compartment represented by the amount of fluid and electrolytes continually exchanged (in and out) by cells with the ISS and by the IVS with the ISS. Other fluids composing the ECS are secretions, ocular fluid and cerebrospinal fluid (Agrò and Vennari 2013).

The TBW represents about 90% of total body weight in neonates. It decreases significantly during the first 6 months of life and reaches adult levels after 1 year of age. The ECS constitutes the main part of TBW and decreases in parallel from 40% in term newborns to adult levels after 1 year of age (Suempelmann et al. 2013). The ECS expansion in neonates is mainly due to higher ISS fluid than adults. This becomes relevant as neonates have difficulty mobilizing fluid and electrolyte excess, potentially leading to pulmo-

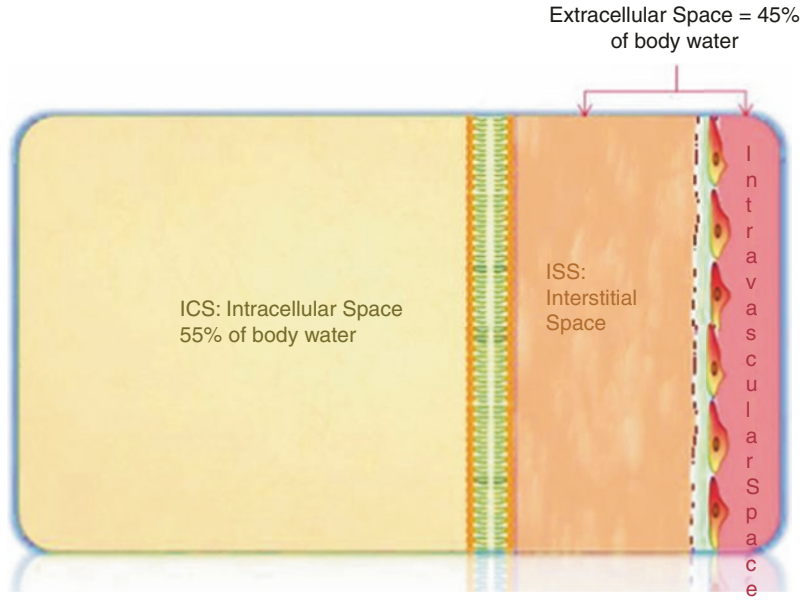

Fig. 1 Body water distribution. (From Agrò and Vennari 2013, pp. 1–26)

nary or peripheral oedema (Sulemanji and Vakili 2013). The composition of the ECS fluid and plasma is similar in neonates, children and adults, but dehydration occurs more rapidly in children because they need more fluids (Roumelioti et al. 2018; Suempelmann et al. 2013) (Table 1).

Soon after birth, kidneys eliminate sodium and water excess in the ECS determining a redistribution of body water and the early postnatal weight loss (a decrease in 5–10% of body weight). The site where most of the sodium exchange is done is in the distal tube (O'Brien and Walker 2014).

Expansion of the ECS by excessive administration of sodium and water, particularly before the postnatal diuresis has occurred, has an adverse effect on outcomes, especially in extremely low birth weight infants (Stephens et al. 2008). A Cochrane review of randomized controlled studies comparing liberal to restricted water (and sodium) intake in preterm neonates showed a significant increase in postnatal weight gain, in the risk of patent ductus arteriosus (PDA) and necrotizing enterocolitis, with an increased incidence of bronchopulmonary dysplasia, intracranial haemorrhage and death (Bell and Acarregui 2014).

A retrospective chart review of 204 premature neonates (gestational age <32 weeks) suggested that restricted water intake in the first 3 days of life (constant calorie intake) was protective for the development of PDA, with a statistical significance observed for analysis accorded for gestational age and severity of illness (Stephens et al. 2008). A randomized controlled trial in preterm newborns (gestational age <30 weeks) showed that early sodium supplementation (4 mmol/kg/day) was associated with delayed postnatal diuresis, delayed reduction in ECS water and increased oxygen requirement at 1 month (Hartnoll et al. 2000a, b). Moreover, excessive sodium administration may result in fluid retention, oedema and hypernatraemia, even in term neonates (Emmerik et al. 2020).

The ICS water does not vary much during infancy, from 30% at birth to 40% in adult (Kight and Waseem 2021).

In adults, insensible water losses (IWL) consist mostly of water lost via evaporation through the skin (2/3) or respiratory tract (1/3). In neonates, IWL from the skin depend on gestational age: the more preterm the infant, the greater the transepidermal water loss. This is due to a higher body surface area/weight ratio and to a thin and fragile skin, poorly keratinized, especially in preterm neonates (Modi 2005). IWL may increase using a radiant warmer or phototherapy, determining a significant effect on fluid balance. In extreme preterm infants, IWL may exceed renal water losses. Evaporation of water from the skin is associated with cooling due to the effect of the latent heat of evaporation (McNeil-Masuka and Boyer 2021). Difficulty in keeping a baby warm may be a sign of excessive IWL. IWL may be reduced by nursing preterm infants <2 weeks of age in a heated humidified incubator (>80% humidity). However, if the baby is taken out of the incubator (for instance, for surgery) or if the incubator is left open for procedures, this protection will be lost. IWL decrease as preterm neonates mature, and ambient humidity may be gradually decreased with time. In ventilated babies, humidification reduces IWL from the lungs. It is also required for babies receiving nasal CPAP or nasal 'high flow' therapy. Postextubation, respiratory IWL may be high if a neonate receives unhumidified O_2 via nasal cannulas. IWL cannot be measured but should be estimated to allow for appropriate fluid prescription. IWL can be estimated using the following formula (Jansen et al. 2012):

Table 1 Composition of the ECS fluid, plasma and ICS fluid

Properties	Plasma	ISS fluid	ICS fluid
Colloid osmotic pressure (mmHg)	25	4	–
Osmolality (mOsmol/kg)	280	280	280
pH	7.4	7.4	7.2
Na^+ (mmol/L)	142	143	10
K^+ (mmol/L)	4	4	155
Cl^- (mmol/L)	103	115	8
Ca^{2+} (mmol/L)	2.5	1.3	<0.001

Fluid and Solute Movements

Fluid and electrolyte balance is both an external balance between the body and its environment and an internal balance between the ECS and ICS, and between the IVS and ISS. This balance is based on specific chemical and physical properties of body fluids, such as ionic composition, pH, protein content, osmotic pressure, osmolarity and colloid osmotic pressure, leading water and solutes to move across the compartments (Agrò and Vennari 2013). Body compartments are surrounded by a semipermeable membrane through which fluids and solutes selectively pass according to the properties of the fluids (Musso et al. 2004). Moreover, water and solute movement between the IVS and ISS is regulated by the capillary endothelium and the overlying capillary endothelial glycocalyx, which together form the endothelial glycocalyx layer (EGL) (Jedlicka et al. 2020).

The glycocalyx consists of glycoproteins and proteoglycans containing glycosaminoglycans attached to the endoluminal surface of the capillary endothelium. It is a dynamic structure continuously degraded and resynthesized, impermeable to large molecules (>70 kDa), and probably it is the main responsible for the oncotic gradient across IVS and ISS (Pillinger and Kam 2017).

Albumin is contained within the EGL, and normal plasma albumin levels are required to assure EGL functions (Young 2012). Furthermore, glycocalyx prevents the endothelial adhesion of inflammatory cells, reducing the risks of an increased endothelial permeability. A glycocalyx damage leads larger molecules to pass from the IVS into the ISS, reducing the IVS–ISS oncotic gradient and increasing the ISS volume with tissue oedema. Various conditions associated to cardiac surgery may potentially destroy glycocalyx: haemodilution, ischaemia and reperfusion damage and inflammation (Young 2012).

Electrolyte Balance

Ionic balance is based on the principle of the 'electric neutrality': the sum of cations must be the same of the sum of anions. In other words, the net sum of the electric charge in the body fluids is zero. Ionic composition of ICS and ECS is different, and further differences exist in the ECS between the IVS and the ISS (Table 1). In clinical practice, the only value directly measurable is the plasmatic concentration of each ion. Generally, this value is considered as a reference to evaluate the presence of electrolyte alterations. The relationship between the ionic plasmatic composition and the neutrality principle is expressed by Gamble gram (Fig. 2). Examining the Gamble gram is immediately evident that the sum of cations (Na^+ + K^+ + Ca^{++} + Mg^{++} + others) is 154 mEq/L and is the same of anions (Cl^- + bicarbonate + proteins + phosphates + sulphates + organic acids). Na^+ and K^+ represent the 94% of all IVS cations, while Cl^- and bicarbonate represent the 84% of all anions. Na^+, K^+, Ca^{++}

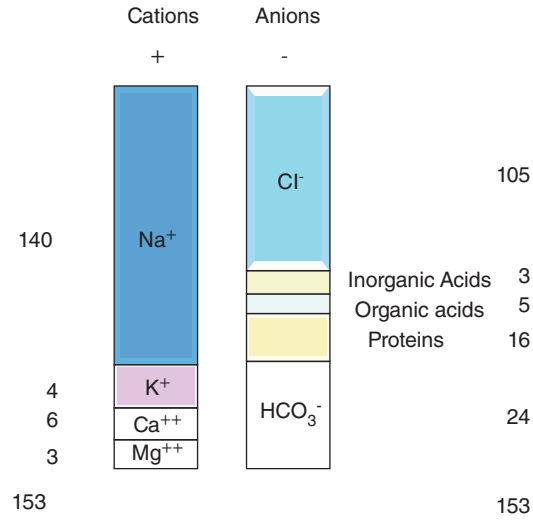

Fig. 2 Gamble gram. Electric neutrality principle: the sum of plasmatic cations is equivalent to the sum of plasmatic anions. (Modified from Agrò et al. 2014)

and Mg^{++} are electrolytes generally measured through laboratory exams, while bicarbonate is only calculated using Henderson–Hasselbalch equation when arterial blood sample is performed (Gamble 1947).

Sodium

Sodium is the most highly represented cation in the ECS and it has a key haemodynamic role: it is the main determinant of ECS volume, contributes to renin–angiotensin–aldosterone system (RAAS) activation and regulates ADH secretion. Sodium concentration determines body fluid osmolarity. Changes in sodium plasma level are responsible for modification in fluid movement across the body space, determining ICS and ECS volume variation. The normal sodium concentration in plasma and the ISS is about 142 mEq/L, and it is higher than the ICS concentration (10 mEq/L) (Agrò and Vennari 2013). Neonates are susceptible to sodium disorders, and both sodium content and water amount administered through IV fluids should be considered carefully (Yang et al. 2021).

Aldosterone secretion is slow to be reduced in the face of a sodium load, for instance, from isotonic fluid boluses, intravenous flushes and drugs, and may result in hypernatraemia or sodium retention with oedema formation. It is recommended that neonates are given sodium-free fluids until after the postnatal diuresis to allow for contraction of the ECS volume (O'Brien and Walker 2014), but inadequate sodium intake thereafter will result in hyponatraemia (Dineen et al. 2017).

This is particularly important in preterm neonates as the renin–angiotensin–aldosterone system (RAAS) is less active, causing a limited ability to retain sodium in the distal renal tubule. Inadequate sodium intake is associated with severe hyponatraemia and poor long-term neurological outcomes in preterm neonates (Yang et al. 2021; Baraton et al. 2009).

Potassium

Potassium is the main cation of the ICS. It plays a central role in determining the resting cell membrane potential, especially for excitable cells such as myocytes. Therefore, it influences the transmission of impulses along the cardiac pacemakers (potentially predisposing to arrhythmias) and the contraction of myocardial cells. It is also involved in a variety of metabolic processes, including energy production and the synthesis of nucleic acids and proteins (Agrò and Vennari 2013). The kidney plays an important role in maintaining potassium balance in the body (Palmer and Clegg 2016).

Potassium is freely filtered by the glomerulus and reabsorption occurs in the proximal tubules. There is some reabsorption in the ascending loop, but the final urinary concentration is determined by the secretion in the distal tubule. In premature neonates, hyperkalaemia is usually evident due the immaturity of the distal tubules. The peritubular and luminal permeability to potassium may also contribute to the physiologic positive balance. A major determinant of potassium balance is cellular metabolism. There is a shift of potassium from the ISS to the ECS immediately after the birth in preterm infants (Lorenz et al. 1997; Bonilla-Félix 2017).

Once the kidney adapts to the extrauterine environment, the increased diuresis facilitates potassium excretion and the regulation of serum potassium levels.

Calcium

Calcium balance in the body is maintained by a well-coordinated mechanism between the gastrointestinal tract, bone and kidneys (Song 2017).

The kidneys regulate calcium reabsorption throughout the nephron via various active and passive processes. Calcium is involved in endocrine, exocrine and neurocrine secretion, coagulation activation, muscle contraction (it has a great inotropic effect), potential membrane depolarization, cell growth and enzymatic regulation and in the metabolism of other electrolytes (especially potassium and magnesium). Calcium may circulate in the plasma bound to albumin and free from proteins. Free calcium may be ionized (physiologically active) or nonionized (chelated with inorganic anions such as sulphate, citrate and phosphate). The amounts of the three forms are altered by many factors, such as pH, plasma

protein levels (hypoalbuminaemia reduces total calcium, but not free fraction) and percentage of anions associated with ionized calcium (blood products contain citrate) (Agrò and Vennari 2013). Although there is a strong correlation between serum total calcium levels and serum-ionized calcium, total calcium can be a poor predictor of calcium status especially in neonates. Low levels of calcium are common in premature infants, but seldom results in tetany or decreased cardiac contractility (Venkataraman et al. 1985; Perino 2020).

Calcium levels tend to stabilize and reach childhood levels by the first week of life (Sulemanji and Vakili 2013).

Phosphorus

Phosphorus is similarly and concordantly regulated with calcium. It has an important role in bone structure and various metabolic processes. The normal plasma phosphorus level is maintained through a balance between intestinal absorption and renal excretion. Renal excretion is the primary mechanism by which phosphorus is regulated in the body (Chang and Anderson 2017).

Parathyroid hormone (PTH) is the most potent hormone that controls urinary excretion of phosphorus. Elevation in phosphorus levels induces the secretion of PTH, which in turn leads to the secretion of phosphorus via the kidneys. Excess phosphorus develops a complex with calcium resulting in a decrease in the production of calcitriol, thereby reducing calcium absorption in the gut (Agrò and Vennari 2013).

Magnesium

Magnesium is the physiological antagonist of calcium. It plays a crucial role in neuromuscular stimulation and modulation of excitable cell activity (membrane-stabilizing activity); it also acts as a cofactor of several enzymes involved in the metabolism of three major categories of nutrients: carbohydrates, lipids and proteins (Reddy 2018; Agrò and Vennari 2013).

Chloride

Chloride is the most important anion of the ECS. Together with sodium, it determines the ECS volume, and it plays a crucial role in acid–base balance (SID approach). It is also responsible for the resting potential of the membrane and action potential, and plasma osmotic pressure (Agrò and Vennari 2013).

Bicarbonate

Bicarbonate is the main buffer system of the blood. It plays a critical role in maintaining acid–base balance (Quade 2021).

Two-thirds of the CO_2 in the human body is metabolized as bicarbonate, through the action of carbonic anhydrase. The equilibrium between CO_2 and bicarbonate leads to the elimination of volatile acid.

When there is an increased concentration of H^+, the system reacts by shifting the reaction equilibrium to the left (towards the production of CO_2); while when the concentration of H^+ is reduced, the system moves to the right, resulting in the production of H^+. The bicarbonate buffer system works 'in concert' with several organs. Bicarbonate has a normal plasma concentration of about 24 mmol/L (Agrò and Vennari 2013).

Acid–Base Balance

The acid–base balance is regulated by a combination of the respiratory, buffer and renal systems. The buffer system constitutes the bicarbonate–carbonic acid buffer, haemoglobin–oxyhaemoglobin buffer, protein buffer and the phosphorus buffer mechanisms. The buffer systems are adapted to serve as the primary mechanism for maintaining acid–base balance in the newborns (Sulemanji and Vakili 2013). With low serum bicarbonate levels and ongoing physiologic demands, the premature infants have a tendency to acidosis. It is known that administration of bicarbonate gives little benefit in comparison of risks, including intraventricular haemorrhage,

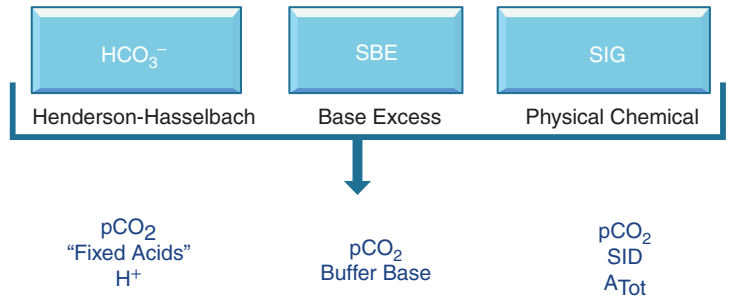

Fig. 3 The three possible approaches to acid–base balance system description. Some factors (i.e., pCO_2) are considered by all the approaches. (Modified from Agrò and Vennari 2013, pp. 1–26)

deteriorating cardiac function and the worsening of intracellular acidosis (ElGkotmi et al. 2017; Aschner and Poland 2008).

However, if strictly needed, bicarbonate should be administered at a very slow rate in order to minimize fluctuations in cerebral haemodynamics (Berg et al. 2010). Term neonates, with the exception of those having congenital complications, usually have a stable physiologic transition from foetal life to extrauterine surrounding. Cardiovascular, respiratory and cerebral hemodynamic mechanisms are in equilibrium with each other and generally result in a balanced acid–base homeostasis. The acid–base balance is maintained closely by complex interactions between the respiratory system and the kidneys. The acceptable values in term infants compared to preterm infants (<28 weeks) are as follows: pH > 7.30 (>7.28), $PaCO_2$ 40–50 (40–50), bicarbonate (HCO_3) 20–24 (18–24) and PaO_2 50–70 (50–65). The respiratory effort in the term infants is almost always stable with marginal predisposition to respiratory acidosis. At the same time, the buffer systems and tubular handling of the term infant kidney are also mature to handle any non-respiratory-induced acidosis within 72 h following birth (Stritzke et al. 2017; Malan et al. 1965).

Classically, there have been three different clinical approaches to acid–base physiology and management:

- The descriptive approach
- The semi-quantitative approach
- The quantitative approach

The first is mainly founded on Henderson–Hasselbalch equation, the second on base excess (BE) and the third on strong ion difference (SID) (Fig. 3). They use distinct variables derived from a set of master equations that can be transferred from one approach to the other two (Agrò and Vennari 2013; Kellum 2005):

Renal Physiology

Renal function is related to the maturation and size of the nephrons, which have the ability to filter the blood and to collect the filtrate. At birth, the kidneys are still undeveloped with reduced ability in reabsorption. Thus, newborns cannot concentrate urine as effectively as adults, and they are unable to excrete large salt loads. After 1 month, the kidneys reach about 60% of their maturation, but the reabsorptive capacity remains lower than in adults. In the first 2 years, the maturity and function of the kidneys increase greatly and reach adult levels (Suempelmann et al. 2013; Bruno 2011).

Renal Blood Flow

Renal blood flow (RBF) changes throughout the years from newborns to adults. It is influenced by the ratio of renal/systemic vascular resistance and the cardiac output (CO). RBF is only about 3–7% of the CO in the foetus (Rudolph and Heymann 1968). After the birth, it is improved consequentially to a reduction in renal vascular resistances and an increase in CO. In the first week of life, RBF is only the 10% of CO. In the neonate, the relation between RBF and kidney weight, body weight and surface area is lower than the adult

(Sulemanji and Vakili 2013). From childhood to adults, a combination of increased renal perfusion pressure and decreased renal vascular resistance leads to an improvement of RBF up to 25% of CO (Musso et al. 2004). The clearance of *p*-aminohippurate has traditionally been used to measure the effective renal plasma flow (ERPF). The ERPF has been reported as:

- <20 mL/min/1.73 m^2 in the premature infant
- 45 mL/min/1.73 m^2 by 35 weeks of gestation
- 83 mL/min/1.73 m^2 in term infants (Musso et al. 2004)

It progressively increases to reach 300 mL/min/1.73 m^2 by toddler age and finally reaches adult rate of 650 mL/min/1.73 m^2 by 2 years of age. This increase is associated with a proportionally higher flow to the outer cortical region. At any age, ERPF may be modified by renal flow autoregulation. However, autoregulation is less efficient in infants, especially at lower baseline values as in newborns (Denic et al. 2016; Musso et al. 2004).

Glomerular Filtration Rate

The determinants of glomerular filtration rate (GFR) are:

- Starling forces across the capillary wall
- Permeability of the glomerular wall
- Total surface area of the capillaries
- RBF (Fig. 4)

GFR is established during intrauterine life, but it is insignificant because the kidneys do not primarily function as a water- and fluid-regulating organ. After birth it significantly increases, as the kidney assumes its role in fluid, water and electrolyte balances (Yared 2004). In the newborn, GFR is about 40 mL/min/1.73 m^2 and it reaches 66 mL/min/1.73 m^2 by 2 weeks of age. Adult levels of 100–125 mL/min/1.73 m^2 are reached at around 2 years of age (Mian and Schwartz 2017; Schwartz et al. 1987).

In addition, maximal urine concentration capacity of the term infants (700 mOsm) does not reach adult levels (1400 mOsm) until 6–12

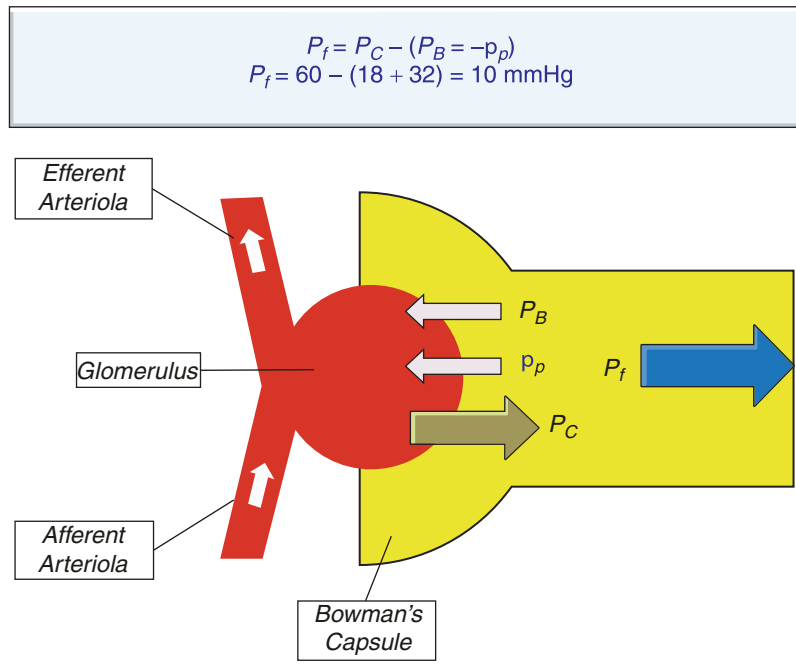

Fig. 4 Determinant of glomerular filtration. P_f filtration pressure, P_c hydrostatic pressure in the capillary (glomerulus), π_p colloid osmotic pressure in Bowman's capsule, P_B hydrostatic pressure in Bowman's capsule

months of age (Rudolph and Heymann 1968). In very low birth weight (VLBW) infants, the increase in GFR is generally reduced than normal weight infants, reaching normal levels later in childhood. Neonates, especially premature, have a limited ability to handle fluid loads: variations in GFR are clinically relevant because they affect fluid and electrolyte homeostasis as well as excretion of drugs (Abitbol et al. 2016; Iacobelli et al. 2007).

A variety of mechanisms are involved in GFR regulation. First of all, macula densa cells of the tubuloglomerular system regulate GFR according to the rate of distal tubular flow and the chloride concentration of the tubular fluid: a high chloride concentration is interpreted as an elevated GFR, while a low chloride concentration as a low GFR. Macula densa cells regulate the afferent arteriole and glomerular capillary tone leading to an adjustment in the GFR (Koeppen and Stanton 2004) (Fig. 5). The myogenic reflex regulates GFR based on renal perfusion pressure. Decreased perfusion pressure leads to a dilation of the afferent arteriole and vasoconstriction of the efferent arteriole (Koeppen and Stanton 2004) (Fig. 5).

Renal perfusion pressure is first compromised in many clinical settings such as cardiac dysfunction, hypovolaemia or septic shock (Post 2017).

In any case (normal, reduced or increased intravascular volume), GFR is maintained by an increase in the filtration fraction in the context of diminished CO and RBF. The myogenic reflex is initially adequate, but as cardiac function continues to deteriorate, it no longer can maintain an acceptable GFR. As a consequence, GFR decreases secondary to diminished renal perfusion leading to accumulation of water and solutes via multiple sodium-retaining systems. Water- and salt-retaining mechanisms are used by kidneys to restore CO and arterial pressure. Depending on the nature and degree of CO reduction, the retention may lead to a vicious cycle of worsening oedema and congestion. However, a drastic RBF decrease may overwhelm the kidney's ability to autoregulate, resulting in a dramatic GFR diminution. When a mild to moderate reduction of renal perfusion develops, GFR may be maintained via various mechanisms that act on the afferent (vasodilator prostaglandins) and efferent (angiotensin II) arteriolar systems. However, any aggravation of this system by

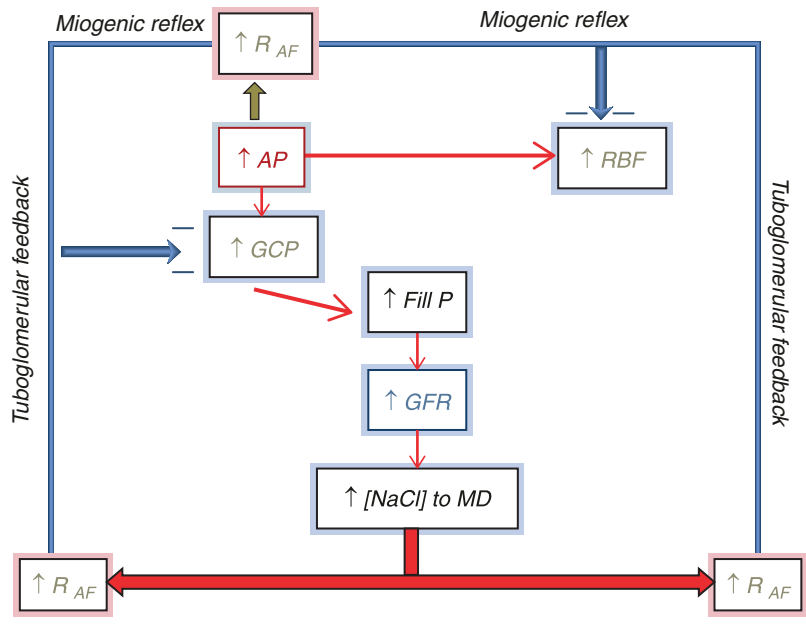

Fig. 5 The tubuloglomerular system and the myogenic reflex

exogenous factors (ACE inhibitors and/or NSAIDs) may produce an important fall in the GFR (Ricci et al. 2011a).

The renin–angiotensin–aldosterone system (RAAS) is activated by secretion of norepinephrine in the peripheral vessels. The RAAS action determines intrarenal vasoconstriction and subsequently diminished RBF with increased sodium retention (DiBona and Sawin1991, 1995; DiBona and Kopp 1997) (Fig. 6). The RAAS is responsible for regulating blood pressure, RBF, fluid and electrolyte balance. Renin is the key component of the system. It is produced in the kidney by the juxtaglomerular cells (Patel et al. 2017).

The mechanism controlling release of renin is well established by late gestation. Hypotension, haemorrhage, furosemide, ACE inhibitors, prostaglandins, vasopressin and atrial natriuretic peptide are all known factors that influence renin secretion. Renin triggers the formation of angiotensin I (ATI) which subsequently gets converted to angiotensin II (ATII) by angiotensin-converting enzyme (ACE). ATII, through plasma membrane receptors ATI and ATII, increases systemic blood pressure determining a vasoconstriction of small vessels with an increase in peripheral resistances. Furthermore, ATII can increase CO through increasing myocardial contractility (Sulemanji and Vakili 2013). ATII has an autocrine effect: it is the primary vasoconstrictor of the renal vessels, modulating reabsorption of sodium and water by kidneys (Kobori et al. 2007). ATII renal action is greatest on the efferent arteriole than afferent, leading to an increase in the filtration fraction with retention of water and sodium (Ichikawa et al. 1984). Moreover, the release of ATII leads to the production and secretion of aldosterone by the zona glomerulosa of the adrenal gland. Aldosterone acts on the mineral corticoid receptors of the kidney, heart, brain, colon and vessel walls. Aldosterone effect on kidney determines sodium retention, which eventually

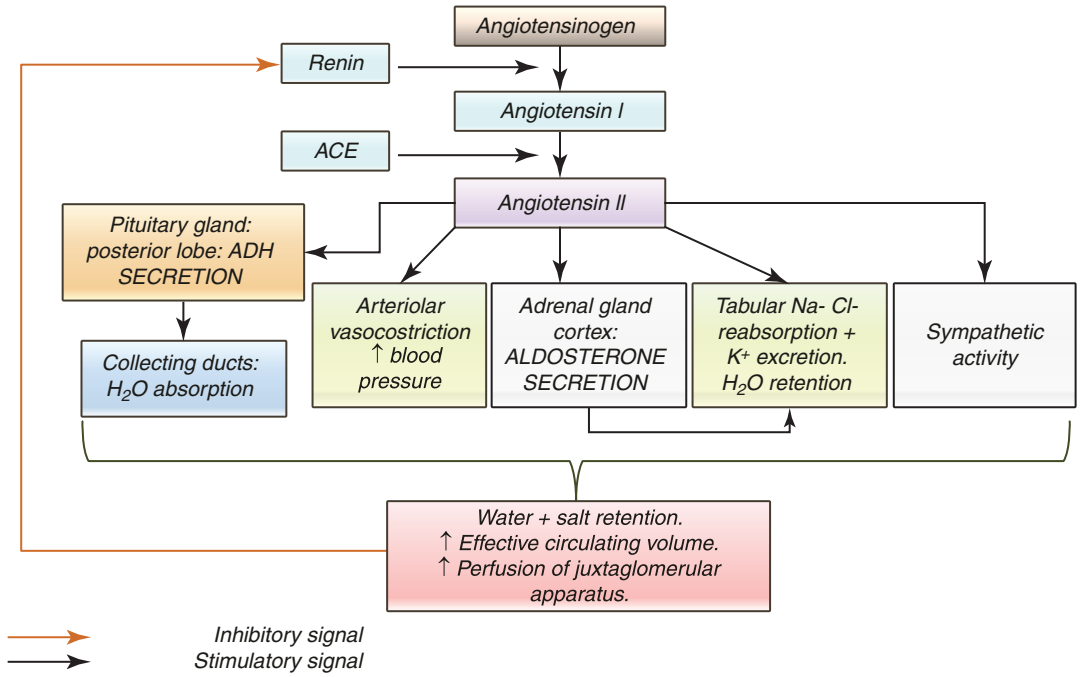

Fig. 6 Renin–angiotensin–aldosterone system: hypovolaemia reduces perfusion of juxtaglomerular apparatus, with renin release. Circulating renin converts angiotensinogen to angiotensin I, subsequently angiotensin-converting enzyme (ACE) acts on angiotensin I converting it to angiotensin II. This hormone increases NSS activity, increases reabsorption of Na and water by kidneys directly and through aldosterone action and determines vasoconstriction and ADH secretion. (Modified from Agrò and Vennari 2013, pp. 71–92)

leads to retention of water (Garty1992; MirabitoColafella et al. 2019).

Components of RAAS are present during early gestation, but their activity and function are somewhat different than adults. RAAS is active in the kidney prior of foetal urine production. This may suggest a role in regulating growth and development of the nephron. At birth, plasma renin activity is increased and continues to stay elevated through infancy. It begins to decline to adult levels by 6–9 years of age (Burdman and Burckhardt 2020; Stalker et al. 1967). Both ATI and ATII receptor expression increase exponentially after birth (Tufro-McReddie et al. 1993), contributing to vasoconstriction of the neonatal kidney. Likewise, there is augmented production of renin, AT and ACE in the postnatal kidney. These effects are counteracted by the postnatal increase in prostaglandins, nitric oxide and kinins which promote vasodilatation and contribute to the maturational increase in RBF (Carey et al. 2000). When CO is reduced, prolonged sodium retention persists with subsequent accumulation of extracellular water.

Aldosterone is one component through which angiotensin regulates sodium reabsorption, influencing fluid and electrolyte balance. The foetal response to secrete aldosterone is less than that seen in adults due to the relative insensitivity of the adrenal gland (Robillard et al. 1982; Almeida et al. 2020).

It is well known that infants with poor cardiac function secondary to congenital heart disease are at risk for acute kidney injury. Mechanoreceptors in the aortic arch, left ventricle and renal afferent arterioles sense systemic arterial pressure and regulate IVS volume. Arterial under-filling activates the sympathetic nervous system with an increase in myocardial contractility, heart rate and peripheral and renal vasoconstriction. Stimulation of the RAAS also contributes to systemic vasoconstriction as well as vasoconstriction of the efferent and afferent arterioles mediated by AT II. Sympathetic stimulation and ATII increase sodium transport in the proximal tubule and deliver less sodium to the distal tubule. This leads to persistent aldosterone-mediated sodium retention in the collecting duct (Fig. 7). Moreover, RAAS activation can have deleterious effects on the heart. In fact, aldosterone increases myocardial collagen deposition, fibrosis, inflammation and remodelling of the heart and blood vessels (Schrier et al. 2010). ATII additionally contributes to left ventricular hypertrophy as well as remodelling.

The antidiuretic hormone (ADH) is secreted from the posterior pituitary in response to severe arterial under-filling leading to osmolarity modification. Stimulation of ADH receptors leads to the expression of aquaporin-2 water channels on the apical surface of the collecting duct, resulting in an increase of water reabsorption restoring osmolarity and volume of IVS (Fig. 7). The persistent activation of these adaptive mechanisms leads to fluid overload, worsening heart failure and decreased renal perfusion (Funayama et al. 2004; Pedersen et al. 2003).

The atrial natriuretic peptide (ANP) increases GFR by constriction of efferent arteriole and dilatation of the afferent arteriole (Staffel et al. 2017). ANP also acts on sympathetic renal effect: it may reverse sympathetic-induced afferent vasoconstriction and potentiate efferent arteriolar vasoconstriction. These effects may suggest a role of ANP in maintaining GFR in heart failure patients, in which ANP values are elevated and renal perfusion pressure is reduced. In addition, ANP counteracts the effects of ATII on the proximal tubule in regard to sodium and water retention: it promotes natriuresis by inhibiting tubular sodium reabsorption (Harris et al. 1987). Moreover, ANP inhibits renin secretion and reduces aldosterone secretion by the zona glomerulosa of the adrenal cortex. It also counteracts maladaptive cardiac hypertrophy and remodelling mechanisms.

The brain natriuretic peptide (BNP) is produced mostly in the ventricular myocardium and has similar action respect with ANP. ANP and BNP react to the effects of the RAAS and sympathetic activation seen in acute cardiac dysfunction. Studies have shown that BNP secretion increase after a left ventricular dysfunction (Wei et al. 1993). BNP's effect is similar to those of ANP (Okamoto et al. 2019).

Prostaglandins are potent renal vasodilators produced by arachidonic acid in many

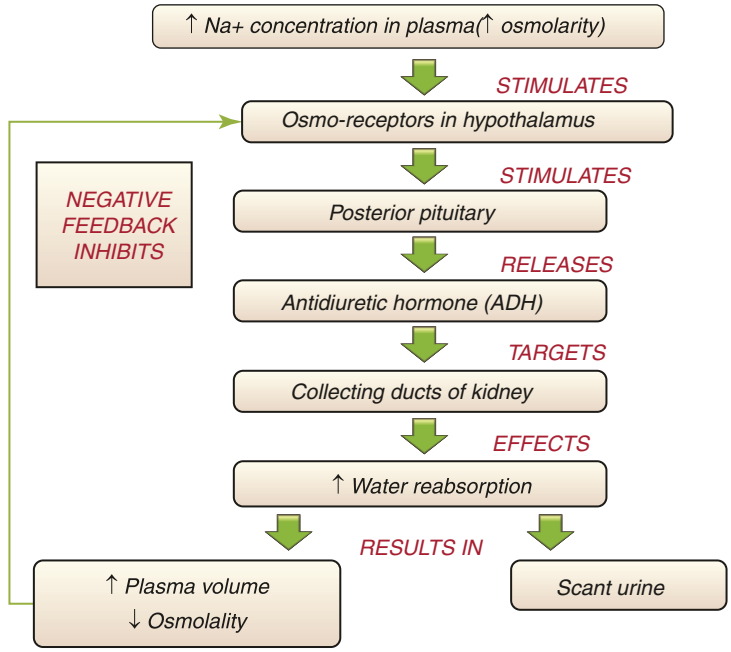

Fig. 7 Mechanism of ADH secretion: when fluid volume decreases, plasma sodium concentration and plasmatic osmolarity increase, leading to hypothalamic osmoreceptor stimulation. The hypothalamus will then stimulate the posterior pituitary gland that releases antidiuretic hormone. ADH will make renal distal tubules able to reabsorb water into the IVS in order to maintain homeostasis of fluid balance. ADH secretion is more sensible to plasmatic osmolarity than circulating blood. (Modified from Agrò and Vennari 2013, pp. 71–92)

cells throughout the body. The major action of prostaglandins is to modulate the actions of vasoconstrictors.

Nitric oxide is an endothelium-derived gas synthesized from the amino acid L-arginine by nitric oxide synthase. It diffuses across the endothelial membrane and enters vascular smooth muscle cells, inducing vasodilatation. In the kidneys, the afferent arteriole is more sensitive than the efferent arteriole to the vasodilator effects of NO. The main action of NO is to modulate the action of angiotensin (Carlström 2021).

Urine Concentration and Sodium Excretion Fraction

Neonatal renal function is theoretically adapted to manage a liquid diet (milk), characterized by a low sodium content. Sodium represents a fundamental element for neonatal growth but although from around 35 weeks' gestation the content of kidneys' nephrons is comparable to that of an adult, there is a reduced ability to concentrate urine, due to short renal tubes (Haycock 2005).

The sodium excretion fraction is increased in the early stages of life and is comparable to that of an adult only from one month of life.

The renin–angiotensin–aldosterone system (RAAS) is responsible for the sodium retention by the distal tubules.

The infants' reduced ability to concentrate urine implies that neonates are very easily subject to dehydration (Bell and Acarregui 2008). Only by a year of age the kidney development is complete (increased complexity and length of the renal tubules during development) and the ability to concentrate urine is comparable to that of an adult.

Congenital Heart Disease Surgery and Acute Kidney Injury

Cardiac surgery (both in adult and paediatric patients) is often complicated by the onset of acute kidney injury (AKI), with an incidence that reaches 30–40%.

AKI can be responsible for adverse outcomes and represents the strongest independent risk factor for mortality (Lassnigg et al. 2004). Even minor degrees of postoperative kidney injuries are connected to a significant increase in morbidity and mortality. The main risk factors for developing AKI after cardiac surgery are summarized in (Fig. 8).

The incidence of AKI in the paediatric population following surgery for congenital heart diseases varies from 3 to 61%, and the mortality from 20 to 79% (Picca et al. 1995; Aydin et al. 2012).

The main cause of AKI is acute tubular necrosis (ATN). Ischaemic insults lead to tubular cell apoptosis and hypoperfusion of the outer medulla. Injured endothelia and tubule cells trigger a Systemic Inflammatory Response Syndrome (SIRS).

The same type of events can also be observed during reperfusion (as explained below).

Hypoxaemia, resulting from preoperative cyanosis or postoperative pulmonary impairment, reduces RBF and GFR, inducing hypotension, hypervolaemia and activation of the RAAS.

The use of nephrotoxic drugs or contrast can induce direct tubular injury.

Intraoperative hypothermia is responsible for renal vasoconstriction and a decrease in GFR.

Positive pressure ventilation (often necessary pre-, intra- and post-operatively) contributes to the impairment of renal function. The decrease of the cardiac output resulting from the decrease of venous return is responsible for the increase of the sympathetic nervous activity.

Sepsis occurrence in the postoperative phase can contribute to the onset of kidney damage via the production of vasoactive mediators that may worsen GFR.

In addition, paediatric patients are more sensitive to the use of inhibitors of ACE inhibitors.

Central venous hypertension, systolic arterial hypotension, pump failure or low cardiac output syndrome, use of inotropic and vasopressor drugs, high-risk complex operation, cyanotic cardiac disease and circulatory arrest in the preoperative period may favour AKI (Pedersen 2012).

One of most important factors that may affect renal function, however, remains cardiopulmonary bypass (CPB).

PREOPERATIVE FACTORS	INTRAOPERATIVE FACTORS	POSTOPERATIVE FACTORS
-iodinate contrast dye	-systemic inflammation	- transfusion
-infection	-ischemia/riperfusion	-IABP
-IABP	-low output state	-inotropic agents
-inotropic agents	-atheroembolism	-infection/sepsis
-low output state	-myoglobina/hemoglobina	-low output state

Fig. 8 Main risk factors of post-cardiac surgery AKI

CPB and Ultrafiltration

It has been known for years that patients undergoing cardiac surgery without extracorporeal circulation (ECC) have a lower systemic inflammatory response and a lower onset of renal damage than those undergoing CPB (Ascione et al. 1999).

Cardiopulmonary bypass requires haemodilution (as a result of circuit priming) and hypothermia and is responsible for the activation of immune response. These conditions can cause tissue ischaemia and lead to organ dysfunction and tissue oedema. Despite the improvements in the CPB's technology and the use of ultrafiltration in cardiac surgery made in recent years, they are associated with multi-organ dysfunction and morbidity and mortality, especially in neonatal age (as a result of small body surface area).

The continuous flow typical of CPB is responsible for systemic inflammatory response and modifications in organ perfusion that can lead to organ damage and RAAS activation.

The exposure of the patient's blood to the non-endothelialized surface of the ECC circuit results in the widespread activation of the innate immune response, the activation of the complement and contact systems and the secretion of proinflammatory cytokines (IL-8, IL-10, TNF-α) (Abu-Omar and Ratnatunga 2006; Asimakopoulos 2001; Warren et al. 2009).

Conventional CPB is also characterized by the presence of an air/blood interface, which contributes to the systemic inflammatory response syndrome (SIRS) (Westerberg et al. 2004).

Reperfusion may worsen ischaemia and the release of oxygen-free radicals.

Ultrafiltration (UF), during and after CPB, is an important tool which mitigates SIRS and multi-organ dysfunction.

During ultrafiltration water and low molecular weight solutes are removed from plasma through a semipermeable membrane. Haemoconcentration allows the removal of excess water and contributes to the reverse of haemodilution with a subsequent decrease of the tissue oedema. Vasoactive substances and inflammatory mediators can also be removed, with the reduction of the severity of the inflammatory response (Bando et al. 1998; Elliott 1999; Gaynor 2001).

Standard paediatric UF techniques are conventional ultrafiltration (CUF, that implies UF during CPB) and modified ultrafiltration (MUF, performed after CPB discontinuation).

During MUF the blood remaining in the venous reservoir is ultrafiltrated, haemoconcentrated and then returned to the right atrium. A roller pump maintains a flow rate of approximately 200 mL/min with a filtration rate of 150 mL/min. Typically, the duration of ultrafiltration is approximately 20–30 min, but has a high institutional variability.

In the present day, CPB management without any ultrafiltration is unthinkable and would not reflect actual clinical practice and these techniques are not mutually exclusive but rather complementary.

During the last decade improvement in CBP, miniaturization of the circuit (Merkle et al. 2004), reduced dependence on hypothermia and less haemodilution resulted in a reduction of inflammation and post CPB oedema with a significant impact in the prevention of AKI (Milovanovic et al. 2018).

Classification and Diagnosis

AKI was historically diagnosed in case of increased serum creatinine levels (SCr) or a reduction in the urine output. Several conditions can influence SCr (age, gender, hydration status, lean muscle mass, muscle metabolism) and to measure a modification of SCr a reduction of about 50% of renal function is needed.

Nevertheless, SCr absolute value and its variations still remain the most widely used method to detect AKI.

The definition of AKI is not univocal.

RIFLE Classification System

In 2002 the Acute Dialysis Quality Initiative (ADQUI, www.adqi.net) created RIFLE criteria in order to define and classify AKI.

RIFLE is an acronym, which stands for "Risk, Injury, Failure, Loss and End-stage" referring to kidney disease group, and it has defined the range of acute renal dysfunction using the so-called RIFLE classification system.

It classifies three grades of increasing severity of acute renal dysfunction and two outcomes (Bellomo et al. 2004b):

- Risk (R)—SCr increased 1.5–2 times baseline OR greater than 25% decrease in GFR OR urine output (UO) of less than 0.5 mL/kg/h for 6 h
- Injury (I)—SCr increased 2–3 times baseline OR decrease in GFR>50% OR urine output of less than 0.5 mL/kg/h for 12 h
- Failure (F)—Scr increased >3 times baseline OR SCr>4 mg/dL OR decrease in GFR>75% OR urine output of less than 0.3 mL/kg/h for 24 h OR anuria for 12 h
- Loss (L)—persistent acute renal failure defined as the need for renal replacement therapy for greater than 4 weeks
- End-stage renal disease (E)—need for renal replacement therapy for more than 3 months

Patients can be classified by GRF or UO criteria.

There is a reasonable correlation between stage of AKI based on RIFLE criteria and mortality.

pRIFLE (modified paediatric version of RIFLE with SCr, GRF and urine output inferior parameters) was proposed to classify AKI in paediatric patients in 2007.

AKIN Classification System

In 2007, the Acute Kidney Injury Network (AKIN) proposed the following criteria for AKI:

- Abrupt reduction (within 48 h) in kidney function = increase in absolute SCr of at least 0.3 mg/dL OR SCr≥(1.5× first value) OR decrease in the UO (documented oliguria <0.5 mL/kg/h for more than 6 h); stage 1 corresponds to the risk class, but it also considers an absolute increase in SCr ≥0.3 mg/dL.
- Stages 2 and 3 define the injury and failure classes, respectively; stage 3 also considers patients needing renal replacement therapy, independently of the stage (defined by SCr and/or UO).
- A correct state of hydration and the exclusion of renal obstruction are necessary for the diagnosis of AKI.
- The AKIN classification requires at least two values of SCr obtained within a period of 48 h, differently from RIFLE and pRIFLE scales (Tables 2, 3, and 4).

The Multi-societal Database Committee for Paediatric and Congenital Heart Disease Classification

In 2008, the Multi-societal Database Committee for Pediatric and Congenital Heart Disease developed consensus definitions used by the STS Congenital Heart Surgery Database—the largest database on paediatric and congenital cardiac operations in the world—for renal dysfunction and renal failure requiring dialysis (Welke et al. 2008). Renal dysfunction was defined as oliguria with sustained urine output <0.5 mL/kg/h for 24 h and/or a rise in creatinine >1.5 times upper limits of normal for age, without the need for dialysis (including peritoneal dialysis and/or haemodialysis) or haemofiltration. Renal failure requiring dialysis was defined as oliguria with sustained urine output <0.5 mL/kg/h for 24 h and/or a rise in creatinine >1.5 times upper limits of normal for age, with the need for dialysis (including peritoneal dialysis and/or haemodialysis) or haemofiltration (Welke et al. 2008).

Table 2 Definition of AKI by AKIN classification

AKIN	Stage	SCr
	I	>0.3 mg/dL
		OR
		↑ 1.5–2 × baseline
	II	↑ 2–3 × baseline
	III	↑ >3 × baseline
		OR
		>4 mg/dL (OR acute raise ≥0.5 mg/dL)

Table 3 Definition of AKI by RIFLE scale

RIFLE scale	Stage	SCr
RISK	↓ GRF 25%	<0.5 mL/kg/h <6 h
	OR	
	↑ SCr 1.5–2 × baseline	
INJURY	↓ GFR 50%	<0.5 mL/kg/h >12 h
	OR	
	↑ SCr 2–3 × baseline	
FAILURE	↓ GFR 75%	<0.3 mL/kg/h 24 h or anuria 12 h
	OR	
	↑ SCr >3 × baseline or ≥4 mg/dL or acute raise ≥0.5 mg/dL	
LOSS	Failure >4 weeks	
ESRD	Failure >3 months	

Table 4 Definition of AKI by pRIFLE scale

pRIFLE scale	eCCI (estimated creatine clearance)	Urine output
RISK	↓ 25%	<0.5 mL/kg/h × 8 h
INJURY	↓ 50%	<0.5 mL/kg/h × 16 h
FAILURE	↓ 75% OR anuria × 12 h	<0.3 mL/kg/h × 24 h
LOSS	Failure >4 weeks	
ESRD	Failure >3 months	

Lab Findings: New Biomarkers

Novel biomarkers for AKI have been developed in recent years, with potentially high sensitivity and specificity. Biomarkers may contribute to early diagnosis in AKI, in the prediction of the outcome, in the identification of AKI aetiologies and subtypes and in the monitoring the response to therapy.

The most promising of these are included in a putative AKI Biomarker Panel, consisting of neutrophil gelatinase-associated lipocalin (NGAL), interleukin-18 (IL-18) and kidney injury molecule-1 (KIM-1).

Human NGAL is a small protein normally involved in innate immunity. It is also present at very low levels in several human tissues such as kidney, lungs, stomach, and colon. NGAL has emerged as a sensitive, specific, and highly predictive early biomarker of AKI in the urine and plasma, after CPB in children. These biomarkers seem to be increased also during systemic infections, inflammatory conditions and malignancies.

IL-18, a proinflammatory cytokine involved in cell-mediated immunity, can be used as marker of injured tubules. IL-18 is more specific to ischaemic AKI, and is affected by chronic kidney disease or urinary tract infections, but can be elevated also in case of endotoxaemia, immunologic injury and cisplatin toxicity.

Urinary IL-18 and NGAL have been proven to represent early, predictive, sequential AKI biomarkers in children undergoing cardiac surgery.

KIM-1 is one of the most highly induced proteins in the kidney after AKI in animal models. Its expression seems to be limited to the injured or diseased kidney, although some nephrotoxins (cisplatin, gentamicin, cyclosporine…) and some clinical states (inflammatory/fibrotic disease,…) can induce its secretion (Devarajan 2008).

Even though novel biomarkers seem to be more helpful to early detect AKI and/or predict the need for renal replacement, and mortality compared to serum creatinine, more comprehensive studies are still required to determine their clinical utility (Beker et al. 2018).

Treatment Course

Fluid Management

Perioperative fluid management in patients with chronic heart decompensation is of utmost importance. The ultimate goal is to maintain perfusion while avoiding fluid overload and fluid management still represents a challenging task.

The amount and the kind of infused fluid play a crucial role in determining or worsening a renal dysfunction.

The maintaining of an adequate cardiac output with no fluid overload (FO) is the first goal of perioperative fluid management in cardiac heart surgery, avoiding primary, secondary and iatrogenic renal dysfunction.

Fluid overload (FO) represents an independent risk of mortality, length of mechanical ventilation and hospital stay (Ricci et al. 2011a). Newborns and paediatric patients are the most delicate patients, especially in case of inflammatory conditions.

Adequate fluid resuscitation is essential to restore cardiac output, systemic blood pressure and renal perfusion in patients with shock secondary to low cardiac output, but fluid responsiveness of cardiac output is dependent both on the volume of the central venous reservoirs and venous tone.

When managing fluid resuscitation, the best strategy may be to ensure a sufficient preload to generate adequate cardiac output.

Goal-directed therapy (GDT) allows physicians to the treatment of hypotension, including volume expansion with boluses of crystalloid or colloid, or the use of inotropes, in order to assure sufficient DO_2 to fulfil the metabolic requirement of the particular patients. This approach may help to determine when fluid resuscitation can safely be stopped, avoiding FO (Agrò and Vennari 2014).

The use of dynamic parameters such as pulse pressure variation (PPV) and stroke volume variation (SVV) can guide fluid management in the perioperative period thanks to the identification of fluid responder and non-fluid responder patients. Unfortunately, these dynamic indices have not been validated during open-chest settings.

Low cardiac output should be managed with a multimodal monitoring and treatment tailored to the single patient and clinical picture trying to obtain the best balance between fluids, inotropes and vasopressors during the whole intra- and postoperative phase.

Goal-Directed Fluid Therapy

Adequate fluid resuscitation is essential to restore cardiac output, systemic blood pressure and renal perfusion in patients with shock secondary to low cardiac output, but fluid responsiveness of cardiac output is dependent both on the volume of the central venous reservoirs and venous tone. When managing fluid resuscitation, the best strategy may be to ensure a sufficient preload to generate adequate cardiac output rather than simply responding to hypotension. Goal-directed therapy (GDT) allows physicians to the treatment of hypotension, including volume expansion with boluses of crystalloid or colloid, or the use of inotropes, only to patients who need them, in order to assure sufficient DO_2 to fulfil the metabolic requirement of the particular patients. This approach may help to determine when fluid resuscitation can safely be stopped, avoiding FO (Agrò and Vennari 2014). Defined haemodynamic variables are necessary to evaluate volume status and to test fluid responsiveness. Filling pressure, central venous pressure (CVP), pulmonary capillary wedge pressure (PCWP), and mean arterial pressure (MAP) are the most commonly used and known parameters to evaluate fluid replacement in cardiosurgical ICU (Kastrup et al. 2007). Despite being easily achieved and their values simply interpreted, they have limited predictive value as indicators of fluid responsiveness due to the different underlying cardiac compliance and value competence (Osman et al. 2007). Many studies have shown that CVP does not adequately reflect preload and fails to predict fluid responsiveness (Agrò and Vennari 2014; Kastrup et al. 2007). In one study PCWP was found to adequately predict fluid responsiveness in 19 patients who have undergone CABG (Bennett-Guerrero et al. 2002). Other studies found a significant CVP and PCWP increase after a fluid challenge, but they do not correlate to an increase in stroke volume (Wiesenack et al. 2001). Moreover, pressure parameters are not very reliable as they are altered by intra-abdominal pressure variation, modification of cardiac compliance, pulmonary resistance and cardiac pathologies (Marik et al. 2008). More recently, the use of respiratory variation of arterial pressure, such as pulse pressure variation (PPV), stroke volume variation (SVV) and continuous cardiac index (CI) to predict fluid responsiveness, has shown some interesting data in both operating room and intensive care units (Teboul and Monnet 2009). Both high PPV and SVV are indicators of hypovolaemia, indicate fluid responsiveness and correlate to the CI increase after

fluid challenge administration (Habicher et al. 2011). This evidence was confirmed in a study on off-pump CABG patients, in which both SVV and PPV strongly correlated to CI improvement after a fluid challenge, with respect to filling pressure (Habicher et al. 2011). As a consequence, dynamic parameters such as PPV and SVV are able to adequately distinguish fluid responder and fluid nonresponder patients and are suitable to guide fluid management in the perioperative period of cardiac surgery, with respect to filling pressure.

The oesophageal Doppler (ED) estimations might be more reliable, even if biased by the need of a learning curve. It allows measurement such as left ventricular end-diastolic area (LVEDA) and the blood velocity at the level of the descending aorta. The flow time in the descending aorta, corrected for HR (FTc normally 330–360 ms), corresponds to the SV. At lower velocities, hypovolaemia should be suspected. FTc correlates with LVEDA (Agrò and Vennari 2014). ED requires shorter operator training than other systems and does not require calibration, but it is difficult to use in awake patients and in a prolonged monitoring, and finally its results may be operator dependent. GDT using ED was shown to improve patient outcomes (Agrò and Vennari 2014).

In the last years, new devices, assessing dynamic and volumetric parameters, have been developed. They are PICCO system and $PiCCO_2$, PULSION Medical Systems, Munich, Germany; FloTrac, Edwards Lifesciences; and LiDCOrapid, LiDCO, London, UK. These devices use transpulmonary thermodilution and/or pulse wave analysis. When the methodologies are used in combination, the validity of pulse pressure analysis depends on periodic recalibration through thermodilution (Agrò and Vennari 2014; Reuter et al. 2010). These systems require invasive arterial lines and a central venous catheter, but they are less invasive than PAC. All these systems have to be compared to the Swan–Ganz or pulmonary artery catheter (PAC), which remains the gold standard, despite its limits. In fact, many clinical trials showed that PAC is not suitable for GDT in the routine perioperative setting. Its use is further discouraged by the invasiveness of the procedure, which exposes patients to complications. In addition, PAC cannot be used without adequate training and experience. Finally, its performance mainly refers to filling pressure values (PVC, PCWP), which have been found to be not so effective in clinical practice. Consequently, its fame in the literature and in clinics has decreased over the years (Agrò and Vennari 2014). Low cardiac output should be managed with a multimodal monitoring and treatment tailored to the single patient and clinical picture trying to obtain the best balance between fluids, inotropes and vasopressors during the whole intra- and postoperative phase.

The maintaining of an adequate cardiac output with no FO is the first goal of perioperative fluid management in cardiac heart surgery, avoiding primary, secondary and iatrogenic renal dysfunction.

Type of Fluid Solution

In 2001, a survey of paediatric anaesthetists suggested that the choice of fluids for plasma volume expansion in infants and children varied by geographical location, with semi-synthetic colloids commonly used and albumin mainly used for neonates (Soderlind et al. 2001). Recently, the evidence about which fluid to use are changed, suggesting caution regarding the use of albumin, the use of semi-synthetic colloids and excessive volumes of intravenous crystalloid in perioperative or critically ill patient (Myburgh and Mythen 2013). At the state of the art, crystalloids are suggested for continuous losses (perspiration sensibilis and urinary output), while colloids are suggested for temporary losses (IVS loss, such as due to haemorrhage) (Agrò et al. 2013a).

Colloids

Colloids are distributed in the IVS, with a larger increase in plasma volume because they contain oncotic particles. They have a longer duration of action, with smaller volumes needed for a specific target volume expansion than crystalloids (Agrò et al. 2013a). If endothelial permeability is intact, colloids are retained in the IVS, with a

subsequent increase of the plasma oncotic pressure and the diffusion of fluids from the ISS to the IVS (Agrò and Vennari 2014). Colloids have a 'contest volume effect': in hypovolaemic patients, they have a volume effect >90% of the volume infused; in normovolaemic patients, two-thirds of the infused volume shifts to the ISS within minutes. Consequently, they should be used only in hypovolaemia, even when there is capillary membrane damage. In fact, in this case, hypovolaemia is connected to the shift into the ISS of protein-rich fluids, with a plasma COP reduction. Colloids that are able to increase COP are needed: their use may reduce ISS overload.

In 2006, Verheij et al. (2006a) showed that following cardiac surgery, volume expansion and cardiac output were significantly higher after colloid infusion than after the administration of crystalloids. He found colloids were approximately five times as efficient in expanding the IVS volume with respect to saline 0.9%. Ley et al. (1990) compared fluid replacement with crystalloids or colloids in patients undergoing coronary artery bypass or valve substitution. Patients treated with HES showed a reduced length of ICU stay than patients treated with normal saline solution. In addition, they required less fluid infusion after surgery and showed better haemodynamic performance than the crystalloid group (Agrò et al. 2013a).

Despite this evidence, colloids have been associated with coagulopathy, and platelet dysfunction, predisposing cardiac surgery patients to postoperative bleeding (in particular when high MW molecules and CPB are involved) and to anaphylaxis (especially gelatins); moreover, colloids may cause tubular damage with renal dysfunction (Agrò et al. 2013a). All colloids can induce kidney injury. The anatomic feature of colloid-induced renal damage is an *osmotic nephrosis-like lesion.* The most likely mechanism of renal dysfunction is a tubular obstruction caused by hyperoncotic urine formation with the storage of colloidal molecules filtered by the glomeruli. This mechanism is further impaired by a condition of dehydration. Another suggested mechanism is an increase in plasma oncotic pressure, with secondary renal macromolecules accumulation. Adequate hydration using crystalloids may prevent this injury (Agrò et al. 2013b). The proposed risk factors for colloid-related kidney dysfunction are age (older patients have a higher risk), hypovolaemia, previous kidney alterations (chronic or acute injury due to other causes) and other comorbidities (such as diabetes and others conditions causing direct or indirect renal alterations). Other risk factors are the type of colloid administered (higher MMW and MS) and the total amount infused per kg of body weight (Agrò et al. 2013b). Clinical evidences of the renal effects of colloid use (especially hydroxyethyl starches) are not uniform, and there is still intense debate as to whether there is truly a critical creatinine level for their administration. Up to some years ago, the use of low MMW and low MS hydroxyethyl starches (HES) was thought to be relatively safe on renal function with respect to other colloids. More recently, many issues have been relieved by literature. Initially, the administration of the newest-generation HES was suggested to reduce the risk of short-term and long-term renal injury (Agrò et al. 2013b; Mitra and Khandelwal 2009). In a study on brain-dead kidney donors, Blasco et al. (2008) compared HES 130/0.4 and HES 200/0.62. At 1 month and 1 year post-administration, they found better effects on renal function (lower serum creatinine) with HES 130/0.4 than with HES 200/0.62 (Feng et al. 2006). The use of fourth-generation HES seems to cause much less harm than older-generation HES, even in patients with previous renal impairment. The infusion of 500 mL of HES 6%/130/0.4 did not cause any kidney damage in volunteers showing mild-to-severe renal dysfunction (Agrò et al. 2013b; Jungheinrich et al. 2002). In a review comprising 34 studies (2607 patients), HES was compared with other fluids. According to other studies, the results evidenced an increased risk of acute renal dysfunction, of long-term renal damage and mortality with HES (even third- and fourth-generation HES), especially in patients with sepsis (Agrò et al. 2013b; Perner et al. 2012; Myburgh et al. 2012). On the basis of these evidences, HES use (included modern HES) has been restricted in Europe, with specific reference to patient with renal dysfunc-

tion or undergoing dialysis. Their use remains justified in case of severe hypovolaemic shock. According to the recent literature, the newest-generation HES seems to be the better colloidal solutions with respect to kidney oncotic damage while assuring an adequate volume replacement. However, the influence of HES on kidney function remains controversial, and large studies are still needed to evaluate the incidence of acute kidney injury with HES in patients without sepsis, directly applying the RIFLE criteria, by precisely measuring the GFR and urine output together with creatinine and NGAL (Young 2012; Agrò et al. 2013b). The need for studies with a specific subset of patients (i.e., cardiac surgery patients) is crucial in the perioperative management of population with a high risk of AKI, such as congenital heart disease patients, considering colloid use is largely diffused in the intra- and postoperative setting (i.e., CBP priming).

Crystalloids

Crystalloids are mainly distributed in the ISS, with less effectiveness in maintaining plasma volume, because they do not contain oncotic particles (Agrò and Vennari 2014). Their duration of action is short, with large volume needed for a specific target volume expansion (Rackow et al. 1983). Their infusion dilutes plasma proteins, thus reducing the COP. Consequently, there is a diffusion of fluids from the IVS to the ISS. This fluid shift increases when vascular permeability is altered, increasing interstitial oedema. A relationship between the administration of high fluid volumes and increased mortality has been reported in cardiac surgery patients (Pradeep et al. 2010). According to the literature, the use of crystalloids for volume stabilization in patients with circulatory shock is related to a higher risk of altered lung function because of pulmonary oedema (fluid overload, referred to as 'Da Nang lung' based on the large number of cases in the Vietnam war) (Agrò et al. 2013a). In particular, the use of crystalloids seems to be less appropriate in patients with reduced myocardial function. Animal studies on acute normovolaemic haemodilution with Ringer's lactate vs. HES demonstrated that HES group presented a significant increase in cardiac output. Moreover, the microscopic study of left ventricular wall revealed the destruction of myofilaments, and mucosal gastric pH was significantly reduced (index of hypoperfusion) in the Ringer's lactate group (Otsuki et al. 2007). CBP with crystalloids has also been associated with postoperative myocardial oedema and cerebral dysfunction with respect to colloids (Iriz et al. 2005). On the other hand, Ringer's solutions were found to not increase pulmonary water volume with respect to dextran 70, after CABG procedures, with no difference on PO_2/FIO_2 (Karanko et al. 1987). Similar results were found in a more recent study comparing 0.9% saline, 4% gelatin, 6% HES 200/0.5 and 5% albumin in a sample of major vascular surgery: no difference was found in PaO_2/FIO_2 ratio and in pulmonary leak index among the groups (Verheij et al. 2006b). When evaluating the effect of different types of fluid replacement therapies, one of most important factors that have to be taken into account is the electrolytic composition. For many years, many clinicians have preferred 'balanced salt solutions' such as Hartmann's or Ringer's lactate in anaesthetic practice. Normal saline contains a higher than physiological concentration of sodium and chloride ions, which may result in hyperchloraemicacidosis and adverse effects on renal or immune function (Myburgh and Mythen 2013), leading to increased vascular tone and a reduction in GFR. So, plasma-adapted and plasma-balanced solutions have a lower risk of AKI, even in cardiac patients, as well as bleeding risk and inflammation response (Agrò et al. 2013a). An observational study of patients in an adult ICU where there was a change from high chloride-containing solutions (0.9% saline, gelatin, albumin in saline) to restricted chloride-containing solutions (PlasmaLyte, Hartmann's, chloride-poor 20% albumin) suggested the low chloride-containing solutions were associated with less acute kidney injury and need renal replacement therapy (Yunos et al. 2012). Similarly, review of a large database of adults undergoing open abdominal surgery showed fewer major complications (blood transfusion, acid–base disturbance, postoperative infection and renal impairment) and improved mortality in

those who received a balanced salt solution (PlasmaLyte) compared with 0.9% saline (Shaw et al. 2012).

Concerns Regarding Paediatric Patients

According to Holliday and Segar (1957), for half a century, the administration of hypotonic fluids with 5% glucose added was considered the gold standard for maintenance fluid therapy in children. Recently, many authors have found the wide use of such fluids causing serious complications, such as hyponatraemia or hyperglycaemia and, more rarely, resulting in permanent neurological consequences or death (Duke and Molyneux 2003).

Two main factors lead to the development of perioperative hyponatraemia: the stress-induced ADH secretion, which decreases the body's ability to excrete free water, and the use of hypotonic solutions as a source of free water. Infants are particularly susceptible to hyponatraemia-related complications, because they have a reduced Na-K-ATPase activity and their brain size/cranial vault ratio is higher (Ayus et al. 2008). Severe hyponatraemia may become a very dangerous condition, leading to a shift of water from ISS into neuronal cells, with subsequent increase in brain volume, leading to cerebral oedema, brainstem herniation and death. All of these sequels can be avoided by the use of balanced electrolyte solutions containing both a physiological osmolarity and electrolyte composition with metabolic anions (acetate, lactate, or malate) as bicarbonate precursors for acid–base stabilization (Sumpelmann et al. 2010). Infants have higher metabolic requirements than adults, potentially leading to perioperative lipolysis and hypoglycaemia. Hypoglycaemia can result in cerebral metabolism and blood flow alterations (Sieber and Traystman 1992) and subsequently in long-lasting neurodevelopment impairment, if unrecognized or undertreated. Administering a 5% dextrose solution in the perioperative period can prevent hypoglycaemia, although these solutions often cause hyperglycaemia because of stress-induced insulin resistance (Welborn et al. 1986). Hyperglycaemias may damage the brain, because of increased lactate levels, leading to intracellular acidosis that compromises cellular functions (Bailey et al. 2010). The literature suggests the use of isotonic solutions with a reduced dextrose (i.e., 1–2.5%) concentration to avoid the above-mentioned consequences of hypoglycaemia/lipolysis and hyperglycaemia in children (Sumpelmann et al. 2011).

Parental Nutrition

In the postoperative phase, one of the major factors affecting fluid balance is parental nutrition (Ricci et al. 2011a). In most cases, more than 60% of total postoperative fluid administered result from parental nutrition. Undernutrition is a serious risk for patients with chronic heart diseases (CHD), both in the pre- and postoperative phase. Postoperatively, surgical stress causes a great amount of energy wasting. Moreover, undernutrition can be exacerbated further by fluid restriction and AKI occurrence (Zappitelli et al. 2008). Inadequate nutrition provision might be associated with decreased patient survival rate in CHD patient, even if there are no studies that confirm it.

Monitoring Daily Fluid Balance

Daily fluid balance should be accurately monitored in postoperative care, avoiding a positive fluid balance. Alternatively, fluid balance might be monitored by daily measurement of patient's weight. An interesting recent weight-based determination of FO status in PICU patients requiring RRT showed that weight-based definition of FO is useful in defining FO at CRRT initiation and is associated with increased mortality in a broad paediatric critically ill patient population (Selewski et al. 2011). Many studies in other critically ill paediatric patient populations with acute renal failure have recently demonstrated that nonsurviving patients have greater degrees of FO at the initiation of RRT, even when corrected for their severity of illness (Ricci et al. 2011a). The prevention of FO is thus an important clinical goal for critically ill patients.

Pharmacologic Management of Fluid Overload

Conventional treatment of FO in the ICU involves the use of diuretics. In the recent years, novel evidence regarding newer agents is available, which may serve as primary or adjunct agents in achieving negative fluid balance.

Dopamine

Historically, low-dose or 'renal-dose' dopamine (1–3 μg/kg/min) was used as medical management of AKI, in the attempt to increase renal blood flow and enhance urine output, throughout the stimulation of D-1 renal receptor. However, multiple studies and meta-analyses have demonstrated that renal-dose dopamine is ineffective in AKI in adult patients (Lauschke et al. 2006).

Loop Diuretics

Loop diuretics are the most used in the critically ill patients, and furosemide is by far the most popular one. It can be administered both in continuous infusion and in bolus. Compared with bolus administration, the continuous infusion has been demonstrated to be generally more advantageous: it results in an almost comparable urinary output with a much lower dose, less hourly fluctuations and less urinary wasting in sodium and chloride (Luciani et al. 1997; Singh et al. 1992). Furosemide use is associated with side effects, the major of which are electrolyte disturbance (hypokalaemia and hyponatraemia), metabolic alkalosis with hypochloraemia and diuretic resistance. In particular, the last effect consists in an absolute or relative inefficiency of diuretic standard dosing. It derives from heart failure per se (inability to reach the optimal peak intraluminal levels of drug), hypoalbuminaemia (that causes less intravascular bindings of the diuretics and less delivery to the proximal tubular cells), hyponatraemia (hyperaldosteronism, vasopressin production and less free water excretion), and the so-called braking effect (decreased responsiveness to diuretics due to histological modifications of loop and tubular cells). A few strategies have been developed to overcome diuretic resistance: use of continuous infusion, increase dosage of loop diuretics, use of combined therapy to block sodium reabsorption, correction of electrolyte balance, metabolic derangements and excessive vascular depletion. Not infrequently, diuretics may be associated with adverse outcome: in the adult population, their use does not prevent the occurrence of AKI, and sometimes it has been associated with increased mortality rates (Mehta et al. 2002). However, it has been shown that furosemide use has a protective effect on 60-day mortality, except when adjusted for fluid balance, suggesting that the benefit of furosemide in critically ill patients is derived from the reduction in fluid balance (Wiedemann et al. 2006).

Finally, a recent study proposed the association between hypertonic saline solution and furosemide, administered simultaneously, showing better outcomes when compared with furosemide administered alone (Liu et al.2021).

Nesiritide

Nesiritide is a recombinant form of human BNP, with effects on the regulation of fluid balance and vascular resistance. As mentioned before, there are two most important natriuretic peptides in cardiac setting: atrial natriuretic peptide (ANP) and brain natriuretic peptide (BNP). ANP, synthesized and mostly stored in the atria, causes diuresis, natriuresis and vasorelaxation and inhibits the release and action of aldosterone than ADH. Brain natriuretic peptide (BNP) is a hormone secreted in the ventricles, in response to ventricular wall stretch caused by hypertrophy or volume overload. It promotes natriuresis and diuresis and induces vasodilatation and antagonizes the effect of antidiuretic hormone and aldosterone throughout dedicated receptors in the vascular endothelium, myocardium and kidneys, antagonizing the effect.

In congenital heart surgery patients, an increase in early postoperative BNP levels has been reported, particularly after repair of tetralogy of Fallot, intracardiac left-to-right shunts and extracardiac Fontan completion (Costello et al. 2004). Moreover, increasing in BNP levels has been associated with increased CPB times and increased aortic cross clamp times (Costello et al. 2005). The mechanism by which CPB

impairs the biological activity of the natriuretic hormone system is not known. Decreased biological activity and poor responsiveness of the natriuretic hormone system might play a role in the development of fluid retention after CPB (Costello et al. 2005).

Nesiritide works on several sites. In the heart, it has a lusitropic effect, acting on intracellular substrates to reduce cytosolic calcium, so causing myocytes relaxation. In the kidney, it increases GFR, and consequently diuresis, by afferent arteriolar vasodilatation and efferent arteriolar vasoconstriction. Indirectly, it augments diuresis inhibiting the effects of the sympathetic nervous system and angiotensin II on proximal tubular sodium absorption, blunting aldosterone production and inhibiting the effect of vasopressin at the medullary collecting duct (Costello-Boerrigter et al. 2003). All these physiological effects lead to the therapeutic benefits of venous, arterial and coronary vasodilatation with a decrease in excessive preload and afterload, resulting in increased cardiac output. So, nesiritide has a therapeutic benefit in adults with congestive heart failure (CHF) and is currently approved for use in acute congestive heart failure (Aronson and Burger 2002; Batool et al.2021).

Similarly, it can have positive effect on low cardiac output syndrome (LCOS). Data suggest that, as well as increasing urine output, it may decrease pulmonary vascular resistance and central venous filling pressure, having a favourable trend in cardiac index and systemic vascular resistance (Hiramatsu et al. 1998). It is also associated with improved fluid balance when associated to routine inotropes and diuretic therapy (Mahle et al. 2005). Moreover, preliminary data propose that the infusion of nesiritide has favourable renal and haemodynamic effects after CPB in adults (Hayashi et al. 2003) and children on extracorporeal membrane oxygenation (Smith et al. 2005) and with CHF (Feingold and Law 2004), even if there are limited studies in children thus far (Moffett et al. 2006).

At least, caution regarding the use of nesiritide in adults as a sole diuretic agent has recently been advised.

Fenoldopam

Fenoldopam is a selective D-1 receptor partial agonist, registered as antihypertensive agent. It promotes the relaxation of vascular smooth muscle, particularly the renal and splanchnic arteries. In the kidney, it increases RBF, tubular sodium excretion and urine output, by blunting aldosterone. It is rapidly titratable, with an elimination half-life of less than 10 min. Several reports suggest that fenoldopam infusions provide renal protection after CPB and during critical illness in adults (Halpenny et al. 2001). Regarding paediatric postoperative cardiac population, data available are limited and do not confirm the adults' results (Villarreal et al. 2021; Ricci et al. 2008b). It is possible that neonatal kidneys are relatively resistant to D-1 receptor stimulation, due to differences in receptor density and affinity and in coupling to intracellular second messengers: neonates might require higher fenoldopam doses to achieve significant clinical effects (about ten times the adult dose) (Ricci et al. 2011b).

Renal Replacement Therapy

In patients with acute renal failure, starting renal replacement therapy (RRT) may be due to different clinical settings. In 2007, the Prospective Pediatric Continuous Renal Replacement Therapy Registry Group (ppCRRT) showed that the main reasons that induce physicians to start RRT in paediatric patients are fluid overload and electrolyte imbalance (Symons et al. 2007). Other causes can be the increase of uraemia, the need to eliminate toxins and the presence of metabolic imbalance. Regarding the choice of RRT modality, intermittent haemodialysis (IHD), peritoneal dialysis, or continuous renal replacement therapy (CRRT) are based on several factors such as:

- Physicians' preferences and expertise
- Patient needs
- Goal of the therapy
- Availability of equipment
- Cost

Table 5 Conventional criteria for initiation CRRT

Indication	Description
Anuria	Negligible urine output for 6 h
Severe oliguria	Urine output <200 mL/12 h
Hyperkalaemia	K^+>6.5 mmol/L
Severe metabolic acidosis	pH <7.2 despite normal or low CO_2 in arterial blood
Volume overload	Especially pulmonary oedema unresponsive to diuretics
Pronounced azotaemia	Urea concentration >30 mmol/L or creatinine concentration >300 μmol/L
Complication of uraemia	For example, encephalopathy, neuropathy, pericarditis

Most used criteria to start RRT are presented in Table 5. Recent indications suggest a wider use of RRT in paediatric and adult patients with AKI than in past years (Picca et al. 2008). This is particularly important especially when the fluid balance cannot be properly controlled with diuretic therapy. In these patients, the early use of RRT prevents or limits FO, allowing adequate nutritional support without worsening the accumulation of fluids. FO is associated with increased mortality in patients receiving CRRT (Bagshaw et al. 2009). It is suggested that RRT should be started within the first 48 h of ICU admission in critically ill AKI patients (Ricci et al. 2011a). Although there are no specific recommendations for RRT in patients without AKI, there is a wide consensus that RRT can improve the prognosis of patients with multiple organ failure (MOF). Goldstein et al. (2005) suggested that the benefit received from the RRT is due to the prevention of FO. They reported that prognosis of patients with MOF was significantly better for patients with less than 20% of FO versus greater than 20% of FO at CRRT initiation. However, regarding the time of starting RRT, international recommendations are not very clear. In this field, the term 'early' or 'late' are both related to the time from ICU admission to CRRT start or to the severity of metabolic alterations present at CRRT initiation (Bellomo et al. 2012).

In 2007, Palevsky reviewed 11 studies from 1961 to 2006 evaluating the timing of initiation of RRT based on the blood urea nitrogen (BUN) level. In the studies analysed, the cut-off BUN value for early initiation ranged from <60 to 150 mg/dL and for late initiation ranged from >60 to 200 mg/dL (Palevsky 2007). In Liu's report of the Project to Improve Care in Acute Renal Disease (PICARD) study (Liu et al. 2006), a better prognosis was found when RRT was started with a BUN <73 mg/dL ($P < 0.0001$) and when CRRT was the initial RRT modality ($P < 0.0001$).

In the literature, there are no data regarding the timing of initiation of RRT based on a BUN level in paediatric patients. Instead, in the last decade, FO was recognized as an independent predictor of mortality in paediatric patients with AKI. In 2001, Goldstein et al. analysed the outcome of children receiving CVVH (Goldstein et al. 2001). They reported a formula to calculate the percentage of FO:

$$\%\,\text{FO at CVVH initiation} = \left[\frac{\text{Fluid In} - \text{Fluid Out}}{\text{ICU Admit Weight}}\right] * 100\%$$

Patients with less FO at the time of CRRT initiation had a better outcome. Similarly, an interesting recent weight-based determination of FO status in PICU patients requiring CRRT reported that weight-based determination of FO is related to increased mortality in a broad critically ill patients (Selewski et al. 2011). In 2009, Hayes et al. showed an OR death of 6.1 when FO was >20% upon initiation of CRRT (Hayes et al. 2009). They also reported a better outcome when CRRT was started with <20% FO, in terms of shorter need of ventilatory support, shorter PICU stay and increased renal recovery rate. Most recently, Sutherland et al. reviewed the ppCRRT Registry data: FO was found to be associated with the mortality in paediatric patients receiving CRRT (Sutherland et al. 2010). Patients with <10% FO upon initiation of CRRT had a signifi-

cantly lower mortality rate compared to patients with an FO between 10 and 20% and FO >20%. The multivariate regression analysis revealed a 3% increase in mortality for each 1% increase in FO present at CRRT start.

Regarding the timing of discontinuation of CRRT, even in this field, the indications are not clear. At the state of the art, there have been no precise recommendations to determine when to discontinue RRT. Usually, RRT is discontinued after renal function has recovered, the electrolytes and metabolic balance have normalized, and the urine output is enough to maintain a negative fluid balance. In 2009, Uchino et al. (2009) reviewed the current practice for the discontinuation of CRRT in 54 adult centres in 23 countries. They concluded that a urinary volume of >436 mL/day without diuretics or >2330 mL/day with diuretic therapy may be used as a threshold to stop RRT. If confirmed, these data may be a valid indication in the future.

In paediatric patients, two dialysis modalities are most frequently used: peritoneal dialysis and continuous renal replacement therapy.

Peritoneal Dialysis

Peritoneal dialysis (PD) is an RRT using patient's peritoneum as a semipermeable dialysis membrane. Fluid is introduced through a permanent catheter in the abdomen and flushed out either every night while the patient sleeps (automatic peritoneal dialysis) or during the day (continuous ambulatory peritoneal dialysis). The peritoneal membrane is vascularized. Solutes move thanks to a concentration gradient between the blood and the dialysis solution. This process called diffusion is also dependent on the molecular size of the solute and the effective surface area and permeability of the peritoneal membrane. Ultrafiltration of water across the peritoneal membrane occurs primarily due to the osmotic gradient generated by the glucose concentration in the dialysis fluid. This technique presents the main advantage to be easy to use, it does not need vascular access (often complicated in infants), and it is generally better tolerated than haemodialysis in haemodynamically unstable patients. However, peritoneal dialysis can be complicated by obstruction of the peritoneal dialysis catheter. Drainage from the peritoneal dialysis can be disrupted due to catheter kinking, fibrin clots or omental wrapping. Furthermore, it was observed that PD is less efficient than haemodialysis in restoring water, electrolytic and metabolic balance. This is true, especially with regard to water removal, with direct consequence on fluid balance. Given these limitations, the early application of PD in order to achieve the prevention and treatment of FO is presently accepted (Alkan et al. 2006). PD also presents limited efficiency in depurative function (Ricci et al. 2008c). In particular it does not provide adequate removal of molecules, and it is not the optimum choice in cases of patients with severe life-threatening hyperkalaemia who require rapid reduction of serum potassium. Another important limitation of PD is that in case of haemodynamic instability, the application of high dialysate volumes is difficult, because changes in atrial conformation, mean pulmonary artery and systemic pressure have been observed (Dittrich et al. 2000). Because high dialysate volumes may not be tolerated in critically ill infants, a PD prescription of 10 mL/kg, previously defined as 'low-volume PD', is commonly used during neonatal RRT (Morelli et al. 2007). In a recent study, the role of prophylactic peritoneal dialysis has been evaluated. It was shown that patients in the PD group had a greater negative fluid balance and decreased levels of IL-6 and IL-8, suggesting removal of inflammatory cytokines by PD. Moreover, these patients had lower inotropic needs, despite typical concerns for negative haemodynamic effects. Finally, the results were statistically significant for decreased duration of mechanical ventilation in the PD group (Sasser et al. 2014).

Continuous Renal Replacement Therapy

CRRT is one of the techniques of extracorporeal dialysis. The use of extracorporeal dialysis is recently increasing, according to the explained

limitations of PD, especially in critical post heart surgery patients (Jander et al. 2007) (Table 6).

Extracorporeal dialysis can be used with several modalities, such as intermittent haemodialysis, continuous haemofiltration or haemodiafiltration. The choice is influenced by many factors, including the goals of dialysis, the advantages and disadvantages of each modality, and institutional resources. Intermittent haemodialysis may be not well tolerated from paediatric patients, especially in those with haemodynamic instability (Flynn 2002), because of its rapid rate of solute clearance (Sadowski et al. 1994).

CRRT is an extracorporeal blood purification therapy used in case of acute or chronic kidney disease intended to replace the lost function of kidneys, aimed at being applied for 24 h a day (Ronco and Bellomo 1996). CRRT provides slow and balanced fluid removal that even unstable patients—those with shock or severe fluid overload—can more easily tolerate. Both adult and paediatric patients can undergo CRRT therapy, and it can be adapted quickly to meet changing needs. However, there are special considerations to take into account when prescribing therapy to smaller patients. The use of CRRT requires a central double-lumen veno-venous haemodialysis catheter. Having functional vascular access is critical for the success of all modalities of renal replacement therapy. Normally, a seven French double-lumen haemodialysis catheter is wide enough in diameter to achieve adequate blood flows for dialysis while minimizing risk of clots in the extracorporeal circuit. Typical locations for placement include the internal jugular, subclavian or femoral veins. In the past, the preferred site for haemodialysis catheter was considered the subclavian vein, but recently it was observed that subclavian access increases the risk for subclavian stenosis and may compromise placement of an AV fistula in the future. So internal jugular vein is generally considered the best access (Ronco and Ricci 2015). The femoral vein is not ideal because increased abdominal pressure could affect blood flow rates. Femoral access is also the most difficult to keep sterile.

Table 6 Differences between PD and CRRT

Advantages		Disadvantages
CRRT	Better haemodynamic stability	Greater vascular access problems
	Fewer cardiac arrhythmias	Higher risk of systemic bleeding
	Improved nutritional support	Long-term immobilization of patient
	Better pulmonary gas exchange	More filter problems (ruptures, clotting)
	Better fluid control	Greater cost
	Better biochemical control	
PD	Easy to perform	Risk of peritonitis
	Does not require vascular access	Catheter problems (obstruction, kinking, fibrin clots, omental wrapping)
	Does not require heparinization	Difficult to optimize ultrafiltration
		Does not provide efficient removal of water
		Both ultrafiltration and solute clearance are slow

One of the main problems that occur with the use of CRRT is the formation of clots in the extracorporeal circuit that necessitate the discontinuation of treatment and the replacement of the entire extracorporeal circuit. Activation of the clotting cascade is due to the contact between circulating blood and artificial surfaces. Repeated changes of the haemofilter result in loss of blood for the patient. This is the reason why anticoagulation remains an area of intense research regarding the use of RRT. Both heparin and citrate are used as anticoagulation, and both have been shown to achieve comparable filter survival (Brophy et al. 2005). However, despite small doses of heparin are used, the anticoagulant effect, especially in critically ill patients, can be significant. Regarding citrate, patients with liver dysfunction may develop citrate toxicity, and then citrate presents a hepatic metabolism.

Normally, the initial blood flow setting ranges from 4 to 5 mL/kg/min. Recommended dialysate or replacement fluid rate is typically 2000–3000 mL/1.73 m^2/h. Ultrafiltration rates typically start at 1–2 mL/kg/h.

Regarding the best CRRT modality to support AKI in paediatric patients, it was recently shown

in vitro that haemofiltration and haemodialysis have the same purification performance at the low blood flow typically used in paediatric patients (Parakininkas and Greenbaum 2004). Even if CVVH at low blood flows used in paediatric patients may result in an excessive haemoconcentration and formation of clots, however haemofiltration is considered to have a better clearance capacity of medium- and small-weight solutes than haemodialysis. For this reason, finally, CVVH is preferred to CVVHD RRT of paediatric patients. During the treatment, a careful monitoring should be applied, because—even if the continuous therapy has less impact on haemodynamic than intermittent one—still small changes in blood flow rate can cause significant changes in the haemodynamic one. Also, the formation of clots and the consequent need to change the circuit can result in the loss of blood that in paediatric patients may be significant. Furthermore, it is important to continuously monitor electrolyte balance, because at the initiation of CRRT, many dangerous electrolyte disturbances may occur.

Finally, ECMO is a commonly utilized technique to support post cardiosurgical respiratory and cardiac failure. The use of CRRT circuits to ECMO, in series, has been recently reported as an effective solution for renal dysfunction treatment during CRRT (Ricci et al. 2011a).

Electrolyte Management

Sodium

In the cardiac surgery patient, sodium overload is the most common alteration due to fluid administration and to the surgical stress response (increased level of aldosterone and cortisol). In this case, it is accompanied by hypervolaemia and fluid overload, with interstitial oedema (Young 2012). Hypernatraemia may be also due to a loss of hypotonic fluids. Renal losses may be caused by furosemide use, osmotic diuresis (severe hyperglycaemia, uraemia, mannitol overdose), pre-existing renal diseases and the development of ATN (polyuric phase). In these cases, sodium losses are associated to water losses, with a reduction of IVS fluid and the presence of signs and symptoms of hypovolaemia (Agrò and Vennari 2013). Less frequently, hypernatraemia may be due to a loss of free body water (hypernatraemia due to sodium concentration). In this case, EVS volume is preserved. The most frequent cause of normovolaemic hypernatraemia is the lack of an adequate restoration of perspiratioin sensibilis, especially when it is increased (i.e., patients with fever).

In the postoperative period, many cardiac surgery patients may present a reduction of sodium plasma levels, due to a shift of water from ICS to IVS rather than a reduction in total body sodium. The shift is caused by hyperglycaemia (diluting hyponatraemia) triggered by the surgical stress response, by the reduction in insulin production and insulin resistance and by an overload in the bypass pump priming (Young 2012). A similar mechanism may be triggered by mannitol overdose. In these cases, hyponatraemia is accompanied by hypertonicity (plasma osmolarity >300 mOsm/L) (Agrò and Vennari 2013). Other causes responsible for hyponatraemia in the ICU cardiac surgery patient are associated to a reduction of plasma osmolarity (true hyponatraemia). In this case, IVS volume may be normal-increased or reduced (Agrò and Vennari 2013).

Advanced heart failure, severe hypovolaemia and hepatic complications with ascites alter ADH release and the kidneys' capacity to dilute urines, leading to hyponatraemia with IVS volume reduction and interstitial oedema development.

The use of diuretics (especially if inappropriate), and the development of SIADH due to cerebral complications or prolonged mechanical ventilation, may cause normo-hypervolemic hyponatraemia without oedema.

Hyponatraemia with hypovolaemia may be due to cerebral salt wasting (cerebral complications), hypokalaemia, renal losses and extra-renal losses. The most frequent cause of renal losses in the cardiac surgery patient is diuretics use and the development of ATN. Possible extra-renal losses are PONV, gastric suction and diarrhoea (i.e. related to enteral nutrition in long-stay patient). In the critic patient, frequent causes of hypovolaemic hyponatraemia are third-space syndromes.

Potassium

Maintaining adequate potassium levels is crucial for bypass pump separation and to prevent postoperative dysrhythmias. In the perioperative setting, many factors may affect potassium plasma levels in different directions. Generally, factors determining a reduction of potassium levels are predominant; as a consequence, potassium loss must be adequately prevented and managed (Young 2012).

Hyperkalaemia may be the consequence of an increase in total potassium body stores or of a shift of potassium from the ICS to the ECS (Agrò and Vennari 2013).

In the cardiac surgery patient, an increase in potassium is commonly due to ICS shift caused by acidaemia, hypoinsulinaemia and haemolysis and to potassium i.v. load due to cardioplegia (Singh et al. 2021).

In case of postoperative ATN, hyperkalaemia often reflects a reduced renal excretion of potassium due to reduced tubular secretion, rather than a reduced glomerular filtration. Adrenal dysfunction (due to disease or drugs), with reduced aldosterone production, can lead to potassium retention (Agrò and Vennari 2013). Muscular weakness, up to paralysis, is one of the main manifestations of hyperkalaemia. Cardiac signs are increased automaticity and repolarization of the myocardium, leading to ECG alterations and arrhythmias. Mild hyperkalaemia may appear with T waves and a prolonged P-R interval; severe hyperkalaemia may cause a wide QRS complex, asystole, or ventricular fibrillation (Hunter and Bailey 2019).

The management of hyperkalaemia includes heart protection and facilitating in ICS redistribution of potassium. Rapid-effect therapies are the administration of calcium gluconate, insulin with glucose (considering patient glycaemia) and correction of acidaemia through bicarbonate administration or hyperventilation. In acute and severe cases (often associated to AKI and development of postoperative complication such as sepsis), CRRT may be indicated considering other electrolytes and acid–base status. Additional therapies are resin exchange, diuretics, aldosterone agonists and β-adrenergic agonists. They act long term, and their use is suitable in long-stay ICU patients who have developed a chronic condition determining hyperkalaemia (Agrò and Vennari 2013; Palmer et al. 2021).

Cardiac surgery patient often presents hypokalaemia, which may be caused by an absolute deficiency of total body potassium stores or by an abnormal shift of potassium from the ECS to the ICS (despite a normal total potassium) (Agrò and Vennari 2013).

In the perioperative setting, a reduction in potassium level is due to augmented catecholamine production with increase skeletal uptake, diuresis caused by hypothermia, furosemide and mannitol use during CPB, and increased cortisol and aldosterone levels due to surgical stress. If hypokalaemia is refractory to intravenous potassium supplementation, concomitant magnesium deficiency should be suspected and treated (Soori et al. 2018).

Other causes may be gastrointestinal loss or renal losses due to diuretic or the development of acute renal damage. Hypokalaemia is always associated to metabolic alkalosis (Agrò and Vennari 2013).

Calcium

Hypocalcaemia is frequent during the intraoperative period. Hypocalcaemia refers to free ionized calcium levels in the plasma. It develops when calcium concentrations are low, but plasma protein levels are normal. As a consequence, it is necessary to know if the calcium value measured is the total plasma value (in this case, it should be adjusted for albumin value) or the ionized fraction (Agrò and Vennari 2013).

In the cardiac surgery patients, hypocalcaemia is generally limited, and it is caused by citrate use, haemodilution, increase of albumin-binding fraction and hypomagnesaemia. In these cases, hypocalcaemia is treated in order to normalize calcium level and to uptake its effects on myocardium (protection and inotropism) and vessels (vasopressor) (Lomivorotov et al. 2020). In the ICU setting, the most frequent cause of hypocal-

caemia is hypoalbuminaemia. Other causes are the development of postoperative renal dysfunctions, hyperventilation, blood transfusion (citrate chelation) and septic complications (the pathogenesis of the mechanisms correlating sepsis and hypocalcaemia is not fully understood) (Young 2012).

Magnesium

Hypomagnesaemia is frequent in the postoperative period after cardiac surgery. It may be triggered by hyperaldosteronism (heart failure, stress response), by calcium alteration (hypercalcemia) and by the use of drugs such as diuretics or adrenergic drugs (Agrò and Vennari 2013). The effects of magnesium deficits are neuromuscular excitability disorders (related to the concurrent development of hypercalcaemia), such as involuntary contraction of the facial muscles, cramps, tetany and arrhythmias or other symptoms mainly related to metabolism, such as morning fatigue. Hypomagnesaemia may lead to hypertension, coronary vasoconstriction and arrhythmias (Young 2012; Kimura et al. 1989; Booth et al. 2003). It may also be characterized by an alteration of consciousness, as demonstrated by confusion, hallucinations and epilepsy.

Magnesium supplementation has been demonstrated to reduce the reperfusion injury, by blocking calcium ingress in myocardial cells and acting as a free radical scavenger (Young 2012; Garcia et al. 1998). In fact, in animal studies, magnesium use has been related with a reduction of infarct size. The timing of administration appears to be very important: no effects have been found when administration is realized early after the reperfusion (Young 2012; Ravn et al. 1999; Herzog et al. 1995). It has been showed how Hypomagnesaemia could be associated to other conditions including cyanotic heart disease and concurrent electrolyte imbalance such as hypocalcaemia and hypokalaemia (Shahidi et al. 2019).

Literature also demonstrated that after CABG, magnesium supplementation reduces the risk of postoperative arrhythmias, i.e., atrial fibrillation, improves the short-term neurological function and may have a significant opioid-sparing effect (Young 2012; Jedwab et al. 2019).

Magnesium inhibits platelets function with a prolongation of bleeding time at 24 h after cardiac surgery. However, a correlation of this effect with an increase of postoperative blood losses is not clear (Young 2012; Gries et al. 1999). On the other side, a reduction in postoperative bleeding and transfusional need after CABG has been showed in patient receiving magnesium (Young 2012; Dabbagh et al. 2010).

Hypermagnesaemia is less frequent in cardiac surgery patient. The most common and probable cause is kidney failure. Haemolysis, hypocalcaemia, adrenal insufficiency, diabetic ketoacidosis, lithium intoxication and hyperparathyroidism are other predisposing conditions. Hypermagnesaemia is characterized by weakness, hypocalcaemia, nausea and vomiting, hypotension, breathing symptoms and arrhythmias up to asystole (Agrò and Vennari 2013; Xiong et al. 2019).

In severe cases, the first line in hypermagnesaemia management is the administration of calcium gluconate, since calcium is the natural antagonist of magnesium. Subsequently, according to renal function, diuretics or dialysis are needed (Agrò and Vennari 2013).

Basis of Pathophysiology Acid–Base Balance in the Postoperative ICU Setting of Cardiac Surgery

Maintaining acid–base balance during and after cardiac surgery is essential for the success of the surgery, especially for procedure requiring prolonged bypass time. As an example, cardiac surgery patients are at high risk for developing arrhythmias: the presence of a neutral pH is necessary to obtain a response to pharmacological and electric treatments. At the same time, acid–base status is considered as an index of adequate perfusion of tissue (i.e., lactate increase, adequate renal compensation) and may modify blood flux distribution. Moreover, pH and pCO_2 variation may influence Hb-curve dissociation reducing

Hb saturation (acidosis, pCO_2 increases) or reducing Hb capacity to transfer O_2 to tissue (alkalosis, pCO_2 decreases) (Agrò et al. 2013a). Literature demonstrated in experimental and clinical studies the influence of pH on vascular tone resulting in possible blood flux redistribution and blood pressure alteration (Celotto 2016).

Both modification of ECS pH (pHe) and ICS pH (pHi) may cause these alterations, through many proposed mechanisms: neurotransmitters release, prostanoids, purines, smooth cells hyperpolarization, NO, changes in intracellular calcium concentration (Franco-Cereceda et al. 1993; Ishizaka and Kuo1996). Moreover, acid–base balance alterations have been related to modification of endothelium activity, with different effects according to the type of considered vessel (Celotto 2016).

On the other hand, cardiac surgery is responsible for profound alteration in acid–base system. At the base of this modification, there are different mechanisms, causing an impact on acid–base balance in opposite directions (Dobell et al. 1960; Gibbon et al. 1950). These mechanisms depend on (Young 2012; Ito et al. 1957; Litwin et al. 1959):

- Type of oxygenator and the type of blood flow during the CPB
- CPB duration
- Kind and duration of postoperative mechanical ventilation
- Hypotension in the postoperative setting (need for inotropes and/or vasoactive drugs, bleeding)
- Kind of fluid used for priming and for liquid management (balanced vs. unbalanced)
- Temperature modifications (hypothermia reduces buffer system dissociation, determining a 'natural alkaline shift', while CO_2 becomes more soluble and pCO_2 is decreased)
- Haemolysis

Metabolic Acidosis

The more frequent alteration of acid–base equilibrium in cardiac patients is metabolic acidosis (Young 2012). It is thought to be due to pre-existing respiratory alkalosis, increased lactate levels, hypoxia, hypoperfusion and ketosis (Dobell et al. 1960; Renew et al. 2016; Klee et al. 2016).

Acidosis induces systemic vasodilatation (included coronary) and pulmonary vasoconstriction (Young 2012). Although vasodilatation may have a positive effect, such as an increase in coronary blood flow, its consequence may be detrimental in patient presenting a cardiac dysfunction after the surgery (Celotto et al. 2016; Clancy and Gonzalez 1975; Ely et al. 1982). Moreover, acidosis reduces the responsiveness to catecholamines, decreasing pharmacological effectiveness of the treatment of postoperative haemodynamic instability and further precipitating patients' conditions. Pulmonary vasoconstriction may increase pulmonary resistance and decompensate the haemodynamic and respiratory status of cardiac surgery patients (Celotto et al. 2016).

In ICU patients, there often is a hyperchloraemic acidosis caused by i.v. fluid infusion, especially when large amounts are needed and unbalanced nor plasma-adapted solutions are used (Young 2012; Morgan 2005; Masevicius et al. 2017).

A severe and prolonged reduction of diuresis and the development of postoperative AKI (especially ATN) may also be the cause of metabolic acidosis due to altered chloride levels and bicarbonate excretion and reduced lactate and other not volatile acids' clearance, especially in patients with pre-existing or precipitating renal dysfunction (Wang and Bellomo 2017; Yuan 2019).

In complicated, long-stay ICU patient, the need for enteral nutrition, gastric aspiration and the development of gastrointestinal dysfunction such as diarrhoea may be other causes of metabolic acidosis with normal AG (Beers 2009).

According to the management of all acid–base alteration, the treatment of metabolic acidosis is to eliminate the underlying cause or causes. As a consequence, an adequate integration between ABG information, patient clinic, patient anamnesis and therapy in course is fundamental.

The use of i.v. bicarbonate is generally indicated when acidaemia (especially severe acidae-

mia) is developing. Sodium bicarbonate use may be more useful in some cases and even deleterious in some others. The current literature suggests limited benefit from bicarbonate therapy for patients with severe metabolic acidosis (pH <7.1 and bicarbonate <6 mEq/L). However, bicarbonate therapy does yield improvement in survival for patients with accompanying acute kidney injury (Ghauri et al. 2019).

When acidaemia is the consequence of a loss of bicarbonate or inorganic acids (AG normal, Cl^- increased, HCO_3^- reduced), the use of i.v. bicarbonate is considered appropriate to restore plasma levels. When acidaemia is due to organic nonmeasurable acids (more frequently lactic acidosis), the use of bicarbonate is controversial: it may be helpful to avoid deleterious consequence of acidity (i.e., protein denaturation), but may cause other deleterious mechanisms (Young 2012; Beers 2009).

Bicarbonate reacts with H^+ producing H_2CO_3 and finally CO_2 that is eliminated through the lungs. In patients under mechanical ventilation, clinicians may modify ventilator parameters in order to optimize the clearance of pCO_2. In patients with spontaneous breathing and in those with pulmonary complication (i.e., postoperative pneumonia, pleural effusion in case of cardiac insufficiency, pulmonary oedema), increasing VCO_2 may be difficult even when using invasive and non-invasive ventilation. As a consequence, pCO_2 retentions with respiratory acidosis may develop aggravating the patient status. The overproduction of CO_2 may aggravate intracellular acidosis because the infused bicarbonate does not pass across the cellular membrane, while the obtained CO_2 freely pass. It reacts with endocellular water finally producing H^+ (Young 2012; Beers 2009).

Sodium bicarbonate administration may depress cardiac function, worsening the haemodynamic status of postoperative ICU patient, especially when there has just been a cause of cardiac failure (Adrogué and Madias 2020).

Considering that bicarbonate is administered with sodium too, the development of hypernatraemia and hyperosmolarity is possible, especially when large amounts of sodium bicarbonate are used (Young 2012; Beers 2009). Finally, the administration of exogenous bicarbonate reduces free ionized Ca^{2+} and K^+ levels that may be deleterious in patients with hypokalaemic acidosis (generally due to renal loss of salts) (Young 2012; Beers 2009).

In mechanical ventilated patient, hyperventilation may be used without bicarbonate administration in order to compensate metabolic acidosis. The consequence is the induction of a respiratory alkalosis that may reduce the hepatic clearance of lactate with a reduction of portal flux, potentially generating liver hypoxia and increase of lactate production (Young 2012; Beers 2009).

In case of postoperative AKI after cardiac surgery, the use of continuous renal replacement therapy (CRRT) should be precociously considered (Young 2012; Beers 2009; Borisov et al. 2019).

In any case, bicarbonate is generally used when (Young 2012; Beers 2009):

- pH <7.2; bicarbonate is <12 mEq/L.
- Hyperkalaemia develops with difficulties to control its value with other treatments.
- Acidosis is symptomatic.
- Patient is waiting for CRRT.

Sodium bicarbonate amount (bicarbonate deficit) may be calculated according to bicarbonate value (Beers 2009)

$$\mathrm{HCO_3^-\ deficit} = 0.4 \,\mathrm{body\ weight} \times \left(\mathrm{goal\ HCO_3^-} - \mathrm{measured\ HCO_3^-}\right)$$

or BE (Beers 2009)

$$HCO_3^- \text{ deficit} = BE\left(mEq/L\right) \times \text{body weight} / 4.$$

Metabolic Alkalosis

Metabolic alkalosis is less frequent with respect to metabolic acidosis in cardiac surgery patients. Generally, it is due to a predominance of bicarbonate levels caused by retention, loss (renal and gastrointestinal), intracellular H^+ shift and/or alkali administration (Beers 2009; Lindner et al. 2013).

In ICU setting metabolic alkalosis is generally caused by acid losses and may be due to secondary hyperaldosteronism caused by hypovolaemia, heart failure, renal artery stenosis (polivasculopatic patients), cirrhosis (patients with hepatic diseases) or renal impairment, HCl and KCl losses due to PONV (especially when high dose of opioid is needed) or gastric suction. Hypokalaemia and hypomagnesaemia are other causes of metabolic alkalosis because K^+ and Mg^{2+} renal reabsorption is realized through H^+exchange (Young 2012; Beers 2009). However, the most frequent cause of metabolic alkalosis in postoperative ICU patients is the use of diuretics (especially furosemide in continuous infusion). Furosemide may lead to metabolic alkalosis through different mechanisms: hyperaldosteronism due to hypovolaemia, Cl^- losses and hypokalaemia (Young 2012; Beers 2009; Tobias 2020).

Other causes of metabolic alkalosis are due to bicarbonate retention overload, such as post-hypercapnic persistent elevation of bicarbonate, generally associated to K^+, Cl^- and volume depletion, lactate or ketoacidosis conversion to bicarbonate (augmented after bicarbonate administration for acidosis) and $NaHCO_3$loading (Young 2012; Beers 2009).

A cause of metabolic alkalosis may be the administration of some kind of antibiotics such as carbenicillin, penicillin and ticarcillin. It should be considered in ICU patients (generally complicated, long-stay patients) with a prolonged therapy with them or with a recent story of protracted use (Young 2012; Beers 2009).

When a metabolic alkalosis persists during the time, it indicates an increased renal reabsorption of bicarbonates. The more frequent stimuli for bicarbonate reabsorption are hypovolaemia (GFR reduction) and hypokalaemia. In fact, in case of hypovolaemia, the kidney increases Na^+ (and water) reabsorption to restore IVS volume. Sodium is reabsorbed as NaCl or $NaHCO_3$. Maintaining IVS volume is more vital than correct alkalaemia; as a consequence, $NaHCO_3$ will be reabsorbed till IVS volume is restored. This mechanism is present only if hypovolaemia is caused by acid fluid losses (vomitus, gastric suction, diuretics). Hypokalaemia leads to a shift of H^+ from ECS to ICS, with stimulus (intracellular acidosis) to H^+ secretion and HCO_3 reabsorption in tubular cells. Frequently two or more causes of metabolic alkalosis may coexist: for example, the use of diuretic may cause hypovolaemia and hypokalaemia (Young 2012; Beers 2009; Tobias 2020).

The treatment of metabolic alkalosis depends on the cause. Metabolic alkalosis involving Cl^- losses responds to administration of fluid containing NaCl. Generally 0.9% saline solution is used. In order to avoid other electrolytic disorders, the infusion of a balanced solution may be suggested. It is recommendable to start the infusion at a rate of 50–100 mL/h and to subsequently increase the rate, according to the estimated and measured losses (Young 2012; Beers 2009).

When metabolic alkalosis is not Cl^- responsive, the correction of K^+ and Mg^{2+} levels is needed. According to Stewart's approach, K^+ deficit should be replaced using KCl. In fact in case of hypokalaemia, the deficit is manly in the ICS: the administered K^+ moves into cells, while Cl^- remains in ECS reducing SID (and SBE), with an acidifying effect (Young 2012; Beers 2009).

The correction of volume and Cl^- and/or K^+ depletion leads to K^+/H^+ exchange, restoring H^+ plasma levels and reducing Na^+ (and consequently HCO_3^-) reabsorption.

Respiratory Acidosis and Alkalosis

Respiratory acidosis is due to CO_2 accumulation caused by a reduced elimination or an increased production.

A reduction in CO_2 elimination is caused by hypoventilation. Frequent causes of hypoventilation in cardiac surgery in the ICU settings may be caused by sedation effects (during weaning from MV and in the immediate postextubation period), neuromuscular blocker effects (fast-track protocols or long-stay patients with protracted curarization), postoperative pain and the development of complications such as cerebral complications or abdominal complications (ascites, abdominal distension), cardiac failure with pulmonary oedema or/and pleural effusion, pneumothorax (post central line positioning or MV related), pneumonia (VAP) and atelectasis. Other causes of hypoventilation may be due to patient's comorbidity such as COPD, OSAS and restrictive pulmonary diseases. These diseases may cause chronic acidosis that may be associated to acute causes (Young 2012; Beers 2009; Osadnik et al. 2017).

Frequent causes of CO_2 overproduction may be hypovolaemia, sepsis and an inadequate artificial nutrition (long-stay patient) with an excess of calories. On the other hand, malnutrition may cause muscular weakness (Young 2012; Beers 2009; Guo et al. 2020).

Finally it is fundamental to remember the detrimental effect of a prolonged MV on respiratory muscles and its effects during MV weaning attempts and the role of oxygen administration resulting in hyperoxaemia and subsequent hypoventilation (Young 2012; Beers 2009).

Treatment is based on the management of the underlying cause and the increase of alveolar ventilation.

Respiratory alkalosis is caused by an increase of alveolar ventilation. Many stimuli may lead to hyperventilation as a physiologic response: hypoxaemia, hypotension, severe anaemia and metabolic acidosis. These causes are often present in the cardiac surgery patient in the ICU setting, especially in complicated cases (Young 2012; Beers 2009; Tiruvoipati et al. 2017).

Other causes leading to respiratory alkalosis are fever and sepsis, pain (insufficient analgesic administration), anxiety and agitation (postoperative delirium, central complication), COPD and pulmonary embolism (Young 2012; Beers 2009).

Finally the most frequent cause of respiratory alkalosis in the ICU patients is iatrogenic: mechanical ventilation. It may be the cause of pseudo-respiratory alkalosis: in cases of hypoperfusion–hypoxaemia, the underlying metabolic acidosis is masked by a CO_2 elimination over the normal rate and due to the mechanical control of alveolar ventilation (Koide et al. 2019).

This alteration may be detected studying the arterial–venous difference in pCO_2, pH and the other ABG markers of metabolic acidosis such as AG and SID (Young 2012; Beers 2009).

A Practical Approach to…

A practical approach to the management of main modification in fluids, electrolytes and acid–base balances should consider that they are interconnected by three principles:

- The electric neutrality principle
- The iso-osmolarity principle
- The neutrality principle

As a consequence, modification in each one of the balances determines modification on both the other two. Clinical scenarios are further complicated by the role of the kidney in modulating each of the three principles.

Fluid Management

1. Postoperative salt and water should be titrated to each patient's individual requirements.
2. Control volaemia using CVP and wedge pressure. The ideal value for atrial pressures is 15 mmHg. CVP may reach 18 mmHg and wedge pressure 20 mmHg in case of:
   (a) Hypotrophy
   (b) Hypocontractility
   (c) Partial obstruction of ventricular outflow
   (d) Pulmonary hypertension

During post-op with significant right atrium dilation, such as anomalous pulmonary vein drainage, the right atrium is overly complacent and CVP oscillates between 5 and 10 mmHg. In surgery with atriopulmonary anastomosis, in the immediate postoperative care, CVP should remain between 18 and 20 mmHg (Joao and Faria Junior 2003; Bignami et al. 2017).

3. The volume of crystalloids offered during the first 24 h may be as follows:
   (a) 40% of basic needs in the form of glucose solution with calcium, for surgery involving CPB
   (b) 60% for surgery without CPB (Joao and Faria Junior 2003)
4. Acute fluid loss (bleeding/drain losses) within the first 12 h post-op should be replaced with equal volumes of fluid (crystalloid/colloid/fresh whole blood). Balanced crystalloids now seem to be the preferred solutions, followed by synthetic colloids (mainly gelatins) and albumin (Protsyk et al. 2017).
5. Avoid excessive volume replacement in response to hypotension or low atrial pressures, because it may be associated with significant increase in total body water particularly in the presence of capillary leak syndrome. Fluid overload may lead to excess lung water and exacerbate pulmonary hypertension, hypoxaemia, V/Q mismatch and cardiac failure. A possible strategy guiding filling is represented in Fig. 9.
6. The choice of replacement fluid should be guided by the haematocrit and the lesion. Patients with a persisting cyanotic lesion will require a higher Hb than those with a non-cyanotic lesion. The following values may be useful:
   (a) Acyanotic heart diseases: Hb 10, Ht 30–35%
   (b) Cyanotic heart diseases: Hb 15, Ht 40–45%
   (c) Blalock–Taussig: Hb 13–14, Ht 40%, in order to avoid obstructing the shunt (Cruz et al. 2015)
7. Consider that fluid administration may modify acid–base status:
   (a) Delusional acidosis
   (b) Hyperchloraemic acidosis (reduces renal perfusion and GFR potentially deteriorating renal function)
   (c) Role of metabolizable anions

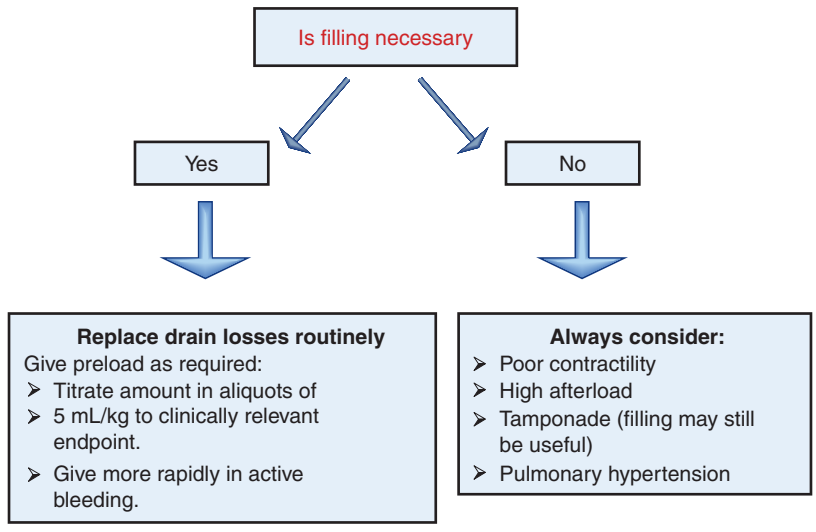

Fig. 9 A suitable filling strategy

Renal Management

1. Hourly urine output should be measured in all patients, preferably by urinary catheter initially. A urine output ≥1 mL/kg/h should be maintained.
2. The overall balance to aim for should be determined by their clinical status.
3. If:
   (a) Diuresis <1 mL/kg/h.
   (b) Haematuria arises.
   (c) Potassium >5 mEq/L.
   (d) Creatinine >1 mg/dL.

   Renal insufficiency may possibly develop.
4. If after the correction of volaemia (Fig. 9) oliguria persists, furosemide is indicated at a dosage of 1 mg/kg up to a maximum of 6 mg/kg/day in an attempt to stimulate diuresis (Cruz et al. 2015).
5. Nesiritide, fenoldopam and dopamine may be used related to patient's individual clinical status.
6. If after stimulation and restricted hydration (including all drugs and infusions, but not boluses of volume expanders/blood products) hypervolaemia remains and urea and creatinine levels are increased, it may indicate RRT (Di Tomasso et al. 2016). The modality, type and settings have been indicated in Sect. 7.

Acid–Base Disorders Management

Eight clinical issues should be solved:

1. pH (acidosis or alkalosis?)
2. pCO_2 (same or opposite direction with respect to pH?)
3. HCO_3^- (same or opposite direction with respect to pH?)

   The answers to these questions may be found using a graphic tool (Fig. 10).
4. Is there compensation according to Boston rules?

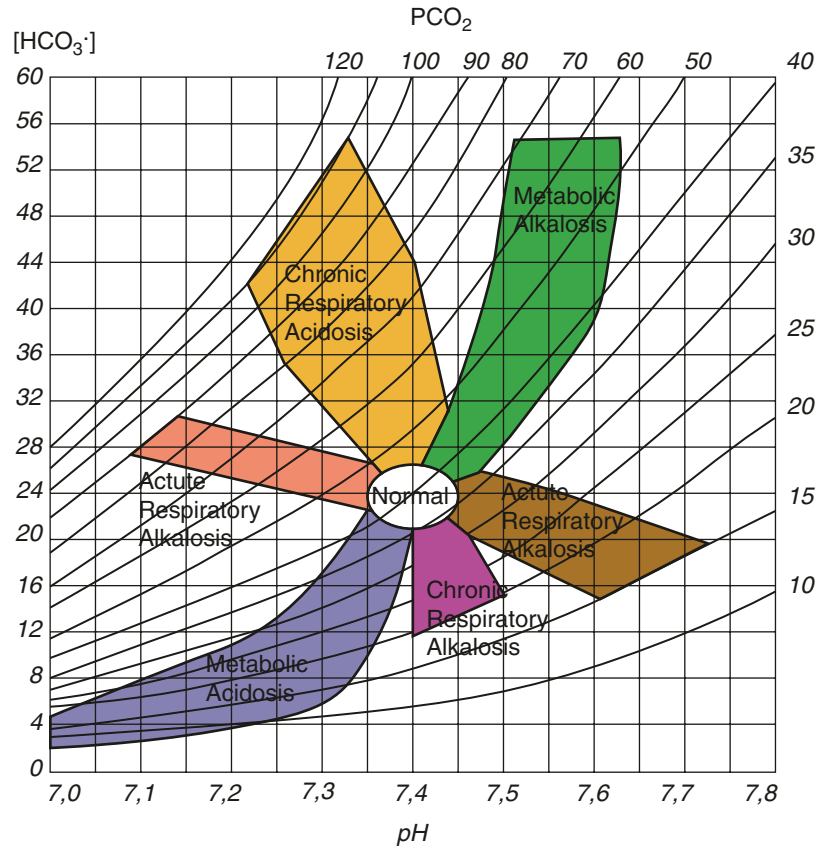

Fig. 10 A graphic tool to rapidly identify acid–base patient disorders knowing pH, $[HCO_3^-]$ and pCO_2

Boston rules and their interpretation are presented in Table 7.

5. Is there an anion gap (AG)? (Fig. 11)

$$AG = \left(Na^{+} + K^{+}\right) - \left(Cl^{-} + HCO_3^{-}\right) = 8 - 16$$

AG evaluation is presented in Fig. 11.

6. If AG is increased, evaluate Delta Gap. It could reveal the presence of more than one acid–base (Fig. 12):

$$\text{Delta gap} = \left(\text{Measured AG} - \text{Normal AG}\right) / \left(\text{Normal } HCO_3^{-} - \text{Measured } HCO_3^{-}\right)$$
$$= \left(\text{Measured AG} - 12\right) / \left(24 - \text{measured } HCO_3^{-}\right) = \Delta AG / \text{"}\, HCO_3^{-}$$

7. What is the SID (strong ion difference) value?

$$SID = \left(\left[Na^{+}\right] + \left[K^{+}\right] + \left[Ca^{2+}\right] + \left[Mg^{2+}\right]\right) - \left(\left[Cl^{-}\right] + \left[A^{-}\right] + \left[SO_4\right]\right) = 38 - 42$$

SID variation according to metabolic disorders is presented in Table 8.

8. Electrolytes

Consider the values of main electrolytes are crucial. As evidenced by SID acid–base, status alteration is always accompanied by electrolyte alteration and vice versa. Examples are:

(a) Hyperkalaemia induced by acidosis (both metabolic and respiratory)
(b) Hypochloraemia in metabolic alkalosis
(c) Hyperchloraemia in metabolic acidosis

The role of chloride levels (mainly modified during fluid administration) is crucial in acid–base status because of its inverse relation with bicarbonate.

Table 7 Boston rules

pH	Disorder	HCO_3	PCO_2	Compensation evaluation	Comment
≤7.38 acidosis	Metabolic	≤24 mEq/L	↓ 1.5 mmHg for each 1 mEq/L of HCO_3 ↓	pCO_2 value higher	Respiratory acidosis
				pCO_2 value lower	Respiratory alkalosis
	Respiratory	↑ 1 mEq/L (acute), ↑ 4 mEq/L (chronic) for each 10 mmHg of pCO_2 ↑	≥40 mmHg	HCO_3 value higher	Metabolic alkalosis
				HCO_3 value lower	No time for compensation or metabolic acidosis
≥7.42 alkalosis	Metabolic	≥24 mEq/L	↑0.7 mmHg for each 1 mEq/L of HCO_3↑	pCO_2 value higher	Respiratory acidosis
				pCO_2 value lower	Respiratory alkalosis
	Respiratory	↓ 1 mEq/L (acute), ↓ 4 mEq/L (chronic) for each 10 mmHg of pCO_2 ↓	≤40 mmHg	HCO_3 value higher	No time for compensation or metabolic alkalosis
				HCO_3 value lower	Metabolic acidosis

From Agrò and Vennari (2013)

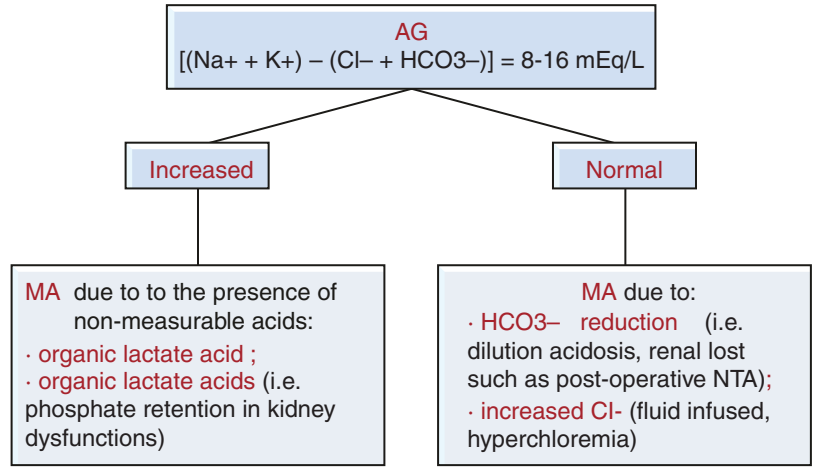

Fig. 11 Evaluation of anion gap. *MA* metabolic acidosis

Table 8 Metabolic disorders according to SID

Metabolic acidosis	↓ SID	↓ SID
	RTA, TPN, normal saline, anion exchange resins, diarrhoea and loss of pancreatic secretions	Ketoacidosis, lactic acidosis, salicylate, methanol
Metabolic alkalosis	↑ SID	↓ A_{tot}
	Loss of Cl^-: vomitus, gastric drainage, diuretics, posthypercapnia, villous adenoma with diarrhoea, mineralocorticoid excess, Cushing's, Liddle's, Bartter's, liquorice; sodium excess; Ringer's, TPN, transfusions	Hypoalbuminaemia (nephrotic syndrome, cirrhosis)

From Agrò and Vennari (2013)

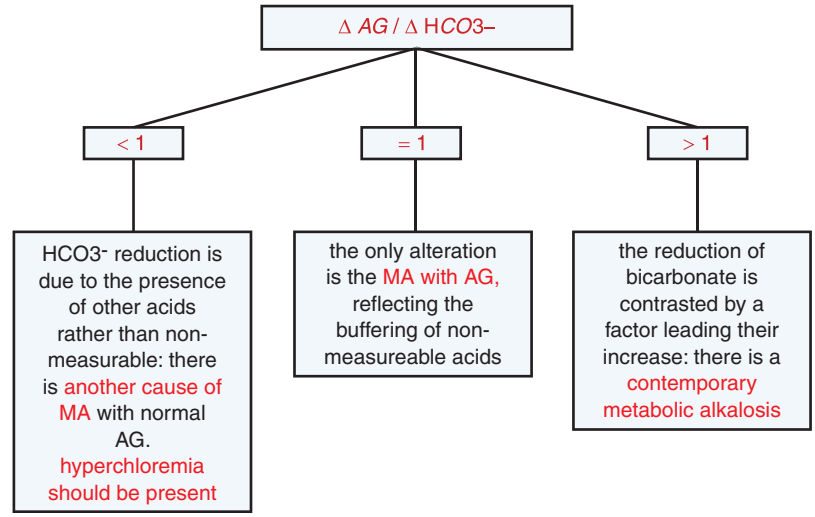

Fig. 12 Evaluation of delta gap. *MA* metabolic acidosis

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Cardiac Intensive Care and Management of Cardiac Arrest in Pediatric Congenital Heart Disease

Rachel Sirignano, Myke Federman, and Neeraj Srivastava

Abstract

Pediatric cardiac intensive care units provide highly specialized care for infants and children with congenital and acquired cardiac disease. There are a number of key elements that ensure this care is at the highest standard. Cardiac patients are at high risk for decompensation and cardiac arrest. Successful resuscitation and survival depend on specific factors including early recognition of deterioration, provision of high-quality cardiopulmonary resuscitation, and awareness of physiologic differences in this patient population. Post-cardiac arrest care is critical to avoiding further deterioration and optimizing neurologic recovery.

Keywords

Cardiopulmonary resuscitation · Cardiac intensive care · Extracorporeal membrane oxygenation

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Pediatric cardiac intensive care has evolved as a distinct subspecialty since the first pediatric intensive care units were established in the 1960s (Epstein and Brill 2005). Similar to how pediatric intensive care units first developed as advanced post-operative and post-anesthesia care units, pediatric cardiac intensive care units developed as the need for specialized care of children after cardiac surgery increased. Today, cardiac intensive care units continue to provide highly specialized care for neonates, children, and adolescents who require cardiac surgery either for congenital or acquired heart disease and also medical intensive care support for children with heart failure and other cardiac medical disease. Success in providing a high standard of care to children in the cardiac intensive care unit depends on several key factors (Balachandran et al. 2010).

Specialized Staff

There are a variety of different models of cardiac intensive care units in term of geography. Cardiac intensive care units (CICUs) can be geographically distinct from the pediatric intensive care unit (PICU) or they can be a unit within a larger unit. Whatever the geographic arrangement, specialized staff is a key component to providing high level care. Physicians, advanced practice providers, nurses, respiratory therapists, and physical and occupational rehabilitation special-

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ists should all have training and experience in caring for children with cardiac disease. This is a key component to providing appropriate medical and post-surgical care and for early recognition of clinical deterioration.

Communication

Clear and open communication is key element to any successful medical environment as well as to high functioning teams. Good communication between cardiac intensivists, cardiologists, cardiac anesthesiologists, and cardiac surgeons is imperative when surgical patients transition between the intensive care unit and operating room. Most cardiac intensive care units (ICUs) have well developed transition and handoff workflows to make sure key information is passed between providers. In addition, front line providers including bedside nurses, house staff, and advance practice providers must be involved in these handoffs to ensure all pertinent information is shared and that specific concerns and clinical plans are communicated.

Monitoring

The ability to monitor vital signs, markers of adequate cardiac output, and advanced physiological information is an important factor in continuous patient assessment and identification of clinical changes. Invasive monitoring of central venous pressure and arterial blood pressure are basic requirements for any unstable patient and additional monitoring of right and left atrial pressure, pulmonary arterial pressure, continuous cardiac output, and pulmonary and systemic vascular resistance are additional advance monitoring capabilities that should be employed as necessary for optimal patient management. The use of near infrared spectroscopy (NIRS) has become a useful adjunct for continuous monitoring of cerebral and somatic tissue oxygenation. Frequent laboratory assessment of arterial and venous blood gases, electrolytes, lactate concentration, and other indicators of adequate cardiac output and tissue oxygenation are also necessary. Currently, tools for predictive analytics are being developed and this will certainly be an integral piece of the ICU of the future (Olive and Owens 2018).

Guidelines and Protocolized Care

The development of clinical guidelines, clinical pathways, and protocols for certain clinical scenarios are paramount to standardizing care in the cardiac ICU. Many cardiac ICUs are part of academic teaching institutions meaning that front line providers, including residents and fellows, often do not have vast experience with complex congenital heart disease. Therefore, the development of basic guidelines helps limit the variability of care day to day. In addition, there are many scenarios that are well suited to protocolized care, such as arrhythmia management, sedation, weaning from mechanical ventilation, post-heart transplant care, extracorporeal support management, and anticoagulation.

Early Recognition of Deterioration

The presence of experienced staff, support of strong communication, high levels of monitoring, and development of guidelines and protocols not only contribute to a consistently high standard of care, but also, and perhaps more importantly, to the early recognition of deterioration and significant changes in clinical status.

Cardiac Arrest and Cardiopulmonary Resuscitation

Approximately 6000 children suffer in-hospital cardiac arrest (IHCA) each year in the United States. While the percentage of patients who have return of spontaneous circulation (ROSC) has improved over the past 20 years to approximately 80%, unfortunately, the percentage of children who survive to discharge after an IHCA has improved to only 45% (Gaies et al. 2012; Topjian et al. 2019). Children with cardiac disease have

higher rates of IHCA than those without cardiac disease (Berg et al. 2016; Lowry et al. 2013). A unifying reason for this difference has not been identified but most likely has to do with the inherent instability and fragility of children with complex cardiac disease. Risk factors for cardiac arrest in patients with cardiac disease include younger age, higher surgical complexity , and other existing comorbidities(Alten et al. 2017; Gupta et al. 2014a). Among children admitted with cardiac disease, surgical cardiac patients have been shown to have higher rates of ROSC and survival to discharge than those with medical cardiac disease (Gupta et al. 2014b, 2016; Ortmann et al. 2011). Some factors that may explain the improved rates of ROSC and survival to discharge in surgical patients are better monitoring and vascular access at the time of arrest and increased use of extracorporeal cardiopulmonary resuscitation (ECPR) in this subpopulation (Gupta et al. 2014b; Matos et al. 2013). Another factor associated with higher rates of IHCA survival is more years of experience of the primary nurse, thought to be secondary to early recognition and more interventions in the pre-arrest phase (Gaies et al. 2012).

High-quality cardiopulmonary resuscitation (CPR) is of the utmost importance when cardiac arrest does occur. Key elements of high-quality CPR include appropriate chest compression rate, adequate compression depth, high compression fraction, or the amount of time compressions are taking place without interruption and adequate release in between compressions (Sutton et al. 2014a). There are two monitoring modalities that can be used as real time markers of the quality of CPR—end tidal carbon dioxide ($ETCO_2$) and diastolic blood pressure measured via arterial line (Sheak et al. 2015; Sutton et al. 2013). In addition, some centers use technology that provides real time feedback regarding chest compression depth and rate that can be useful during CPR.

Physiology of Cardiac Arrest

Majority of cardiac arrest in pediatrics is as a result of asphyxia/hypoxia from progression of respiratory failure, rather than progression of cardiogenic shock and hypoperfusion (Caen et al. 2015; Kleinman et al. 2010). Cardiac arrest, however, is 10 times more likely in children with heart disease than among those without underlying heart disease (Ortmann et al. 2011; Peddy et al. 2007). Among children that arrest in the in-patient setting, almost 60% are mechanically ventilated and ~40% are on inotropes and vasopressors at the time of arrest (Nadkarni et al. 2006). Management should focus on cardiac and respiratory support in the pre-arrest period. Post-operative patients in the cardiac ICU usually have evidence of inadequate oxygen delivery before the arrest phase, unless the arrest is precipitated by arrhythmia or thromboembolic phenomenon. In these patients with hypoperfusion and low cardiac output, early initiation of ECLS should be considered in post-operative period. For children with asystole or pulseless electrical activity, immediate initiation of high-quality CPR is essential, along with simultaneous search of reversible and/or treatable conditions like low cardiac output syndrome (LCOS), tension pneumothorax, cardiac tamponade, electrolyte imbalances especially hyperkalemia, pulmonary hypertensive crisis, or shunt occlusion. The most common terminal rhythm in pediatric patients was brady-asystole (Nadkarni et al. 2006), and asystole and pulseless electrical activity were the most common terminal rhythms in patients with heart disease (Ortmann et al. 2011). Hypoxia and/or hypotension leads to bradycardia which often precedes cardiac arrest. Chest compressions along with ventilation should be initiated in critically ill patients with bradycardia and poor perfusion. National Registry of CPR reports better survival (40.7%), when high-quality CPR was initiated during the bradycardia with pulses and poor perfusion phase, as compared to when CPR was initiated when the terminal rhythm was asystole or pulseless electrical activity (24.5%) (Nadkarni et al. 2006). For patients with ventricular fibrillation (VF) or pulseless ventricular tachycardia (VT), defibrillation in addition to high-quality CPR is indicated.

Mechanics of Resuscitation

In structurally normal hearts, high-quality CPR delivers 30–40% of blood flow to the brain and only

10–30% of blood flow to the heart (Kleinman et al. 2010). The 5 main components of high-quality CPR are: optimal compression rate, adequate chest compression depth, allowing full chest recoil between compressions, minimizing interruptions in compressions, and avoidance of excessive ventilation (Atkins et al. 2015). Standard American Heart Association (AHA)-recommended high-quality CPR is indicated for children with congenital heart disease (CHD); however, the provider must consider special circumstances like open sternum or fresh suture lines.

Current pediatric AHA guidelines recommend an optimal compression rate of 100–120 per minute for all age groups in absence of direct information regarding infants and children. The preferred compression technique for neonates and infants involves 2-thumb, encircling hands technique, with thumbs together compressing the lower third of sternum and fingers encircling the infant's thorax. This technique provides greater depth of compression which results in improved coronary perfusion and higher systolic and diastolic blood pressures than 2-finger technique. For infants and children, recommendations are to provide chest compressions that depress the chest at least one-third the anterior-posterior diameter of the chest, which equates to ~1.5 in. (4 cm) in infants to 2 in. (5 cm) in children. Once the children have reached puberty, it is reasonable to use adult compression depth of at least 5 cm but no more than 6 cm (Sutton et al. 2013; Braga et al. 2009). Compressions are thought to generate blood flow during resuscitation by cardiac pump (compressing the heart between the sternum and vertebral column) and thoracic pump (creating intrathoracic to extrathoracic pressure gradients) mechanism. Although pediatric data are not available, these mechanisms have been well established in adults with CPR using echocardiography (Kim et al. 2008). Failure to allow for full chest recoil keeps the intrathoracic and right atrial pressure high, which in turn decreases the coronary perfusion pressure (aortic end diastolic pressure minus right atrial pressure) and cardiac perfusion during resuscitation. This is usually seen when the rescuer leans on the chest and fails to allow for full chest expansion. There are animal studies linking inadequate chest recoil with decreased cardiac output/index leading to reduced coronary and cerebral perfusion pressures (Zuercher et al. 2010).

Minimizing interruptions to compressions is vital to a successful resuscitation (Sutton et al. 2009). It may be necessary to pause compressions for airway placement, rhythm checks (lasting no more than 10 s approximately every 2 min), administration of shocks and ECLS cannulation (Meaney et al. 2013), but the duration of these pauses should be monitored carefully and kept to the minimum time required. When performing CPR without an advanced airway, it is reasonable for single rescuers to provide a compression-to-ventilation ratio of 30:2 and for 2 rescuers to provide a compression-to-ventilation ratio of 15:2 (Topjian et al. 2020). When performing CPR in infants and children with an advanced airway, it may be reasonable to target a respiratory rate range of 1 breath in every 2–3 s (20–30 breaths/min), accounting for clinical conditions (Topjian et al. 2020). Positive pressure ventilation increases intrathoracic pressure and impedes venous return, and excessive ventilation at rates above these rates can compromise hemodynamics (Sutton et al. 2019).

Monitoring During Resuscitation

In addition to providing AHA-recommended high-quality CPR, we recommend that in a tertiary care ICU setting managing post-operative cardiac surgical patients, providers should continuously monitor the physiological parameters to evaluate the efficacy of resuscitation and individualize therapy as appropriate. Arterial waveform if available during resuscitation provides valuable insight not only regarding systolic (compression) and diastolic (relaxation) pressures, but also the probability of ROSC. In an adult study, a coronary perfusion pressure of at least 15 mmHg was required for ROSC and the survival increased if the pressures were >20 mmHg (Paradis et al. 1990). There is insufficient data for infants and children; however, expert consensus aligns with adult guidelines to keep the coronary perfusion

pressures above 20 mmHg (Meaney et al. 2013). In structurally normal hearts or in patients with corrected biventricular physiology without intracardiac shunts, continuous waveform capnography provides information regarding the pulmonary blood flow as a result of effective chest compressions. If the $ETCO_2$ is low (<15 mmHg), it is reasonable for providers to optimize CPR to increase cardiac output and pulmonary blood flow; however, there are insufficient data to use $ETCO_2$ as a prognostic indicator (Kleinman et al. 2010). In patients with shunt-dependent pulmonary blood flow, significant pulmonary insufficiency or single ventricle physiology, $ETCO_2$ underestimates the cardiac output and becomes challenging to establish target threshold. Data from adult studies also show that higher NIRS saturation during resuscitation also increases the chances of ROSC (Ahn et al. 2013).

Cardioversion and Defibrillation

Children with CHD require more frequent cardioversion and defibrillation as compared to patients without heart disease. For cardioversion in pre-arrest setting, adequate sedation and analgesia can be achieved with short-acting agents; however, in case of cardiovascular collapse it can be performed without sedation or analgesia. General recommendations for cardioversion are same for children with and without CHD (Kleinman et al. 2010); however, modifications need to be made for open chest patients. Either handheld paddles or self-adhesive pads can be used, with anterior-posterior or anterior-lateral pad positioning may be appropriate. For dextrocardiac patients, pads should be placed over the right side of the chest so as to keep the heart between the pads. For an open chest, the position needs to be modified, or internal paddles can be used with sterile precautions. Cardioversion is indicated for atrial flutter or atrial fibrillation; defibrillation for VF or pulseless VT.

For cardioversion of supraventricular tachycardia (SVT) or wide-complex tachycardia with pulse, an initial energy dose of 0.5–1 J/kg is used. If the initial dose is not effective, it can be increased to 2 J/kg. All shock for cardioversion is delivered in a synchronized mode so as to avoid precipitating VF. For VF/pulseless VT, an initial dose of 2 J/kg is indicated. Subsequent doses of 4 J/kg are indicated, and higher doses can be considered, although dose should not exceed 10 J/kg (Kleinman et al. 2010). If internal paddles are used, the dose is 0.6–0.7 J/kg to maximum of 10–20 J/kg.

Adult out-of-hospital resuscitation studies have shown a strong relationship between pre-shock and peri-shock pauses and shock success, including survival to discharge. The pre-shock pause is the interval between last chest compression and shock delivery. The peri-shock pause is the sum of pre-shock pause and interval between shock and start of next chest compression. Pre-shock pause of longer than 20 s and peri-shock pause of greater than 40 s lead to a significant decrease in survival to hospital discharge. Survival fell by ~14–18% for every 5 s increase in these pauses (Cheskes et al. 2011). Although data in pediatrics are lacking, it is likely that prolonged pauses in compressions will be detrimental to survival in children as well. In the fibrillating heart, CPR improves myocardial creatinine phosphate levels, as well as amplitude of fibrillation, both of which lead to improved cardiac energy state thereby improving the shock success (Hoogendijk et al. 2012). To date, no studies have demonstrated improved outcomes with transcutaneous pacing in cardiac arrest.

Airway

Most critically ill post-operative patients have an advanced airway; however, if the child has no airway in place then the decision to intubate and the timing of intubation should be carefully evaluated. Initially effective oxygenation and ventilation can be accomplished with bag and mask. For patients with ineffective oxygenation and ventilation, placement of oral airway or laryngeal mask airway can assist with ventilation. In case of prolonged CPR and in cases where effective oxygenation and ventilation cannot be achieved, insertion of advanced airway is indicated. A nasogastric or

orogastric tube should be placed to decompress the stomach which facilitates with ventilation and also to prevent regurgitation and aspiration (Salem et al. 2014).

Vascular Access

Administration of resuscitation medications through an indwelling central venous catheter is preferred if available. If there is no vascular access, PALS guidelines recommend the use of intraosseous or peripheral access, if it can be obtained rapidly. Placement of central venous access is generally not recommended during resuscitation, and moreover providers need to be aware of vascular abnormalities or occlusion from prior procedures in children with CHD.

Pharmacology

Effective medication delivery during cardiac arrest requires blood flow and delivery of drugs near central veins. High-quality chest compressions are necessary to circulate any drugs during resuscitation. Providers should follow AHA PALS CPR and Emergency Cardiac Care guidelines for drug doses and administrations. For pediatric patients in any setting, it is reasonable to administer epinephrine as the first line medication during resuscitation. Intravenous (IV)/intraosseous (IO) route is preferred as compared to endotracheal tube (ETT) administration. The first dose should be administered as soon as possible or within 5 min of the start of compression, also it is reasonable to dose epinephrine every 3–5 min until ROSC is achieved (Topjian et al. 2020). For shock-refractory VF/pulseless VT, in addition to the above-mentioned epinephrine doses, either amiodarone (5 mg/kg IV/IO bolus up to a maximum of 15 mg/kg) or lidocaine (1 mg/kg) can be administered. In a multivariate analysis of data from the GWTG-R Registry (Get With The Guidelines-Resuscitation), among patients with in-hospital cardiac arrest associated with VF/pulseless VT, use of lidocaine was associated with increased ROSC and 24-h survival; however, neither medication was associated with improved survival to discharge (Dorian et al. 2002; Valdes et al. 2014).

Mechanical Support

The use of extracorporeal life support (ECLS) for treatment of in-hospital cardiac arrest refractory to initial high-quality CPR has been increasing in both adults and children. The body of literature examining the use of extracorporeal cardiopulmonary resuscitation (ECPR) and survival of children with heart disease has been increasing. Multivariate analysis of factors has demonstrated improved survival with the use of ECPR in children with both medical and surgical heart disease. A recent GWTG-R Registry data showed that ECPR was associated with improved survival to hospital discharge and survival with favorable neurological outcome compared to conventional CPR in children with in-hospital CPR >10 min (Lasa et al. 2016). No differences in survival have been reported between operated or unoperated patients, as well as between single or biventricular congenital heart defects (Kane et al. 2010). Observational studies have shown good outcomes in acute fulminant myocarditis patients supported with ECLS (Rajagopal et al. 2010). Survival after ECPR is higher in children with cardiac disease than in those with noncardiac disease. Hospital survival after ECLS in cardiac ICU ranges from 34% to 45%, with in-hospital survival from ECPR being 33–79%, although transplantation may be required in some cases (Joffe et al. 2012). The severity of pre-arrest metabolic acidosis (based on pH and lactic acidosis) is associated with survival and neurological outcomes (Chan et al. 2008). The duration of CPR cannot be used exclusively to guide selection of patients for ECPR as survival with favorable outcome has been demonstrated with conventional resuscitation for >60 min (Raymond et al. 2010). One study showed improved survival of patients placed on ECPR in cardiac catheterization laboratory or ICU compared to other areas (Kane et al. 2010); however, locations vary widely based on institutional practices. We rec-

ommend that ECPR duration of cannulation can be shortened by restricting ECLS deployment to certain areas of the hospital where both equipment and personnel skilled at providing high-quality CPR as well as managing ECLS are available. There is some evidence to show that in pediatric patients, high volume centers (>15–22 patients per year) have better survival than low volume centers (Freeman et al. 2014). Most centers use crystalloid primed circuits for ECPR, at our center we use blood prime for patients less than 10 kg if available so as to prevent excessive hematocrit dilution from circuit volume in smaller patients.

ECPR complications limit the survival, with neurological complications being the most common occurring in at least 20% of ECPR patients (Golan et al. 2014). These complications can result from pre-arrest factors, quality of CPR before ECLS or as a result of complication of ECLS itself.

Mechanical Support in Single Ventricle Patients after Cardiac Arrest

ECLS is being increasingly used to support children in the post-operative period. The Single Ventricle Reconstruction Trial reported 13% incidence of cardiac arrest in the post-operative period after stage 1 Norwood palliation. Because of the difficulty in obtaining ROSC after conventional CPR, half of these patients require ECPR (Tabbutt et al. 2012). Extracorporeal Life Support Organization (ELSO) Registry reported 31% survival among patients supported by ECLS after stage 1 palliation (Ravishankar et al. 2006). The presence of shunt obstruction has been associated with better survival to discharge, whereas failure to separate from cardiopulmonary bypass at the end of the procedure has associated with worse outcomes (Ravishankar et al. 2006). Not surprisingly, longer duration of support has been associated with poor survival, with ELSO Registry reporting no survivors after 10 days of ECLS support (Tabbutt et al. 2012). The use of ECLS in patients with superior Cavo-pulmonary anastomosis (CPA) and Fontan completion pose unique anatomical, technical, and physiological challenges. The presence of elevated systemic venous pressures combined with low systemic blood pressures lead to higher mortality and poor neurological outcomes after cardiac arrest. Retrospective analysis of data from ELSO Registry showed 41% survival to hospital discharge in patients supported by ECLS after superior CPA, and 35% survival to hospital discharge after Fontan operation (Jolley et al. 2014; Rood et al. 2011). It is reasonable to consider pre-arrest use of ECLS in patients with superior CPA or Fontan physiology, due to high mortality and poor neurological outcome after ECPR in these patients.

Special Considerations for Resuscitation in Delivery Room

There are important physiological differences in cause of cardiac arrest in premature infants with lung disease and those with congenital heart disease; however, neonatal resuscitation program recommends to follow similar guidelines. In the event that compressions are required, a total of 90 compressions and 30 breaths (120 events) are delivered in each minute, to balance ventilation and cardiac output (Kattwinkel et al. 2010). Antenatal planning for resuscitation in the delivery room is critical in high-risk CHD patients. Lesions likely to need resuscitation include severe forms of Tetralogy of Fallot (TOF) with absent pulmonary valve, Ebstein anomaly of tricuspid valve, mitral atresia with intact atrial septum, and transposition of the great arteries (TGA) with intact atrial septum. The latter two lesions will require transcatheter or surgical interventions to create an ASD for stabilization. Neonates with obstructed pulmonary veins will likely require mechanical ventilation, but unlikely to require CPR. Newborns with systemic or pulmonary blood flow ductal-dependent lesions will require low-dose PGE1 infusion (0.01 μg/kg/min) in the delivery room. Survival and prognosis are poor in absence of prenatal diagnosis and preplanned intervention.

Special Considerations for Resuscitation in Immediate Post-Operative Period

Majority of patients in the immediate post-operative period have arterial and venous waveform monitoring lines, which can be used to guide and optimize resuscitation techniques. Estimation of coronary perfusion pressure and diastolic blood pressure can help optimize rate and depth of chest compressions. Effective pulmonary blood flow is compromised in setting of valvular insufficiency, single ventricle physiology, and pulmonary hypertensive crisis. In the immediate post-operative period after sternotomy and cardiotomy, there is a greater risk of myocardial and thoracic injury, bleeding, or dehiscence of intracardiac repairs (Miller et al. 2014). In patients with open sternum, direct cardiac massage can be performed; however, there are no data to base this recommendation. Arterial line monitoring can be used to document the effectiveness of this technique (Sutton et al. 2014b). It is important to develop resuscitation strategy for all post-operative patients which include the deployment of ECLS.

Resuscitation in Patients with Mechanical Circulatory Support (MCS)

Absolute number of cardiac arrests in patients on mechanical support has been increasing due to the increasing use of the therapy in patients with end-stage heart failure. Ventricular assist devices have two distinct mechanisms of blood flow: the older rarely used pulsatile-flow and the current generation of continuous-flow devices. Patients on newer generation MCS are in a unique physiological state of stable hemodynamics with pulseless electrical activity, which is referred to as pseudo-pulseless electrical activity. Because of this unique characteristic of blood flow, these patients do not have a palpable pulse so the rescuers need to determine if an unresponsive or mentally altered patient is, in fact, in cardiac arrest or cardiovascular collapse. Conditions altering preload such as hypovolemia, pneumothorax, and cardiac tamponade can all decrease preload leading to circulatory failure. Conditions affecting afterload such as vasodilatory shock states can lead to inadequate tissue perfusion as patients with mechanical circulatory support (MCS) cannot increase their cardiac output in response to low systemic vascular resistance. Device failure can also lead to cardiovascular collapse. The most common causes of pump failure are loss of power and discontinuation of the driveline. All devices have built in safety mechanisms/alarms to alter the provider of pump malfunction. Common problems in these patients include infection, bleeding, pump thrombosis, and stroke. These patients are anticoagulated to prevent thrombosis risk; however, this can lead to significant bleeding risk (Crow et al. 2010). Assessment of tissue perfusion is the most important factor in determining the need for circulatory assistance such as chest compressions. Assess perfusion by skin color, temperature, and capillary refill. If there is inadequate perfusion, assess for MCS malfunction. If the device is functioning properly, chest compressions should be started in the unresponsive patient if mean arterial pressure (Manual BP cuff and Doppler is the recommended approach) and $ETCO_2$ (if mechanically ventilated) are below physiological limits for age.

In summary, there is minimal data regarding effective CPR in patients with CHD. The efficiency of standard CPR is limited in patients with single ventricle physiology, severe valvular insufficiency or pulmonary hypertensive crisis. Moreover, the impact of hemodynamic variables and $ETCO_2$ monitoring during resuscitation are poorly understood. Institutions should develop and implement strategies for placing these patients on ECLS should high-quality CPR be unsuccessful. It is also reasonable to consider deployment of ECLS before cardiac arrest or during early resuscitation.

Post-Cardiac Arrest Care

Stabilization

The key to successful resuscitation and improved post-cardiac arrest outcomes gets underway immediately after ROSC. Early management

starts with stabilization of the patient utilizing the *A,B,C's* of basic life support. More patients may require an advanced airway after ROSC, as the shift in resuscitation emphasizes decreased interruptions during chest compressions rather than pausing to place an endotracheal tube during CPR (Andersen et al. 2016). It is important to ensure hemodynamic stability with good cardiac output prior to establishing an advanced airway, as early post-resuscitation hypotension has been shown to have increased mortality (Andersen et al. 2016; Topjian et al. 2014; Kilgannon et al. 2008). Cardiovascular support can include inotropes (epinephrine, norepinephrine, and dopamine) and/or temporary pacing in the post-operative patient to help augment cardiac output. The myocardial injury incurred during cardiac arrest makes the patient more susceptible to arrhythmias, and anti-arrhythmic medications should be readily available for use (Checchia et al. 2003). Once endotracheal intubation is complete and mechanical ventilation has started, a detailed bedside clinical exam should be completed including a baseline neurologic assessment.

Investigation into Etiology

The next step in post-cardiac arrest care begins with investigation for diagnosing and then treating the cause of cardiac arrest. Myocardial dysfunction is common, occurring in nearly half of all post-cardiac arrest patients and has been associated with higher mortality (Checchia et al. 2003). The cytokine surge during a cardiac arrest state follows a typical pattern seen in septic shock or post-cardiopulmonary bypass, with the peak dysfunction occurring 8 h from the event, and resolving around 48–72 h (Adrie et al. 2002). The child is at highest risk during this time period for a recurring arrest if the proximal cause of arrest is not identified and treated. Examples include fever and on-going shock from sepsis, electrolyte derangements (e.g., hyperkalemia), pulmonary hypertension, acute respiratory failure with hypoxia, or residual surgical lesions (Chandler et al. 2015; Lowry 2012; Marino et al. 2018). Bedside point of care lab draws, and echocardiograms may be sufficient to identify and treat the inciting anomaly. But given the risk of morbidity and mortality for residual cardiac lesions, axial imaging or cardiac catheterization may be warranted to better distinguish any correctable lesions (e.g., cardiac MRI and cardiac CT). Risks and benefits must be carefully weighed with a multi-disciplinary approach (cardiothoracic surgery, cardiac anesthesia, cardiology, and intensive care team) when deciding to return to the operating room to repair any residual lesions during the early post-cardiac arrest phase.

Prevention of Secondary Injury

After treating the precipitating pathophysiology for the cardiac arrest, the next step for recovery includes prevention of secondary injury due to the no flow state of cardiac arrest, low flow state of CPR, and subsequent hypoxia which affects all body systems. The systemic ischemia of cardiac arrest and then reperfusion state of ROSC brings a cascade of cytokines similar to what is seen in septic shock (Adrie et al. 2002). Many studies have investigated modifiable risk factors associated with higher morbidity and mortality in the post-cardiac arrest state. Although the optimal blood pressure has yet to be defined, multiple studies have found that hypotension, or systolic blood pressure less than fifth percentile for age, is associated with higher in-hospital mortality and unfavorable neurological outcomes (Topjian et al. 2014; Kilgannon et al. 2008; Lopez-Herce et al. 2014). Likewise, studies which aggressively treat hyperglycemia in the inflammatory post-cardiac arrest state have shown mixed results, and raise concerns about the long-term effects of hypoglycemia induced by insulin therapy (Agus et al. 2017; Sadhwani et al. 2016; Wintergerst et al. 2006). Similarly, studies have been mixed in outcomes on whether hyperoxia and hypercapnia are associated with higher mortality, and current guidelines recommend aiming for normocapnia and oxygen levels appropriate for the child's underlying congenital heart disease pathophysiology during post-cardiac arrest care

(Topjian et al. 2020; Lowry 2012; Marino et al. 2018).

A large source of morbidity from cardiac arrest and resuscitation is global hypoxic ischemic injury to the brain. Peak cerebral edema is seen in the first 24–48 h during the post-cardiac arrest care. Again, treatment is targeted toward modifiable factors during this secondary injury phase. Studies have shown that persistent hyperthermia is associated with worst neurologic outcomes (Bembea et al. 2010). Unfortunately, the largest trial investigating therapeutic hypothermia (32–34 °C) for in-hospital cardiac arrest (THAPCA-IH) was stopped early due to futility, given that no difference was observed in neurologic outcomes at 1 year survival for patients receiving targeted temperature management (Moler et al. 2017). Close neurologic morning via continuous video electroencephalography (EEG), serial bedside examinations and NIRS, and can help identify evolving brain injury and help with prognostication after the first 24–48 h. Up to two-thirds of electrographic seizures after ROSC are non-clinical, and given the high degree of secondary injury from seizures, continuous video EEG is highly recommended (Sanchez et al. 2013; Abend et al. 2009). ICP monitoring is no longer standard of as aggressive cerebral edema monitoring and therapy in severe hypoxic global ischemia has not shown improved outcomes for survivors. However, imaging modalities to quantify the extent of hypoxic ischemic injury via brain CT and MRI can help with prognostication for outcomes in the first week after cardiac arrest. Investigations are on-going for the benefit of cerebral metabolism monitoring including global end capillary brain tissue oxygenation ($PbtO_2$), or cerebral micro-dialysis catheters (Lee et al. 2014). Although patients may require some level of sedation and neuromuscular blockade during their post-cardiac arrest care, there is insufficient strong data to support a specific class of medications, or guide the practitioner on the duration of analgo-sedation. Risks and benefits must be weighed for decreasing metabolic demand while potentially increasing length of mechanical ventilation and masking clinical seizure activity.

The key to decreasing secondary injury and improving morbidity and mortality for post-cardiac arrest care stems from aiming for normal parameters for patients (euthermia, euglycemia, normal saturations per congenital heart disease physiology, and eucapnia) and strict avoidance of physiologic abnormalities (hypotension, hypoxemia, hyperthermia, hypoglycemia, and seizures).

Cognitive Rehabilitation

Those children who survive IHCA are at a high risk for cognitive, physical, and emotional disabilities. The early plasticity of the child's young brain may help with the improved survival and improved neurologic outcome for a younger patient population post-cardiac arrest (Meaney et al. 2006). However, insufficient evidence exists to guide inpatient or outpatient rehabilitation for survivors of cardiac arrest. At this time, data supports that anoxic brain injury has worst outcomes than what is seen for traumatic brain injury or stroke (Robertson et al. 2002). But given the strong support for improved outcomes after early intensive neurorehabilitation programs for traumatic brain injury patients, it seems practical for the cardiac intensive care team to consult rehabilitation experts after the first 72 h of recovery and post-cardiac arrest care to help create an inpatient and outpatient rehabilitation recovery plan for cardiac arrest survivors (Bedell 2008; Eilander et al. 2005).

Outcomes and the Future

Prognostication and counseling for families with the post-cardiac arrest child is difficult. No single variable has been shown to be reliable and accurate in predicting morbidity and mortality for those children who achieve ROSC (Caen et al. 2015). Although evidence suggests that severe abnormalities early post-ROSC (severe lactic acidosis and hyperglycemia) suggest higher mortality, the true picture typically cannot be seen until after secondary injury has occurred

and quieted about 3 days after the arrest. As noted earlier, about half of patients who achieve ROSC will survive to discharge (Gaies et al. 2012; Topjian et al. 2019). Few studies have investigated the long-term survival and neurologic outcomes for IHCA. The selected few studies published demonstrate 73–86% of survivors to discharge have a favorable neurologic outcome at discharge (Pediatric Cerebral Performance Category 1 or 2) and stayed in that category at 1 year follow-up (Castillo et al. 2015; Zeng et al. 2013; Garcia Guerra et al. 2015).

The development of specialized pediatric cardiac intensive care units and the multi-disciplinary approach for this complex group of patients has led to an increase in ROSC during in-hospital cardiac arrest. The next steps for improving outcomes in our congenital heart disease patients will need to look at all areas of care including early recognition for the pre-arrest state, patient directed resuscitation given complex cardiopulmonary physiologies during the cardiac arrest state, optimization of utilizing technologies for diagnostics and therapies for stabilization of patients, directed approach to minimize secondary injury in the post-cardiac arrest care and continued investigation for long-term follow-up in our cardiac arrest survivors.

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Cardiac Intensive Care and Management of Cardiac Arrest in Adult Congenital Heart Diseases

Marisa Hernandez-Morgan

Abstract

Due to advances in surgical techniques and medical management of patients with congenital heart disease, the number of patients surviving into adulthood is rapidly increasing. Thus, there is an increasing population of adults with congenital heart disease presenting for surgical (both cardiac and non-cardiac) and interventional procedures who require specialized care. According to current estimates there are now more adults with congenital heart disease (CHD) than pediatric patients in the United States, 1.4 million versus one million respectively. Given that over 90% of children born with CHD today are expected to survive to adulthood (Stout et al. 2016), it is imperative for the intensivist and any practitioner who will be involved in the ICU care of these complex patients to be familiar with the comorbidities frequently seen and the basic management strategies. The world of mechanical circulatory support (MCS) for the adult with congenital heart disease is a young field but with growing evidence to support its use.

Keywords

ICU management ACHD · Mechanical circulatory support ACHD · eCPR · ECMO · Cardiac arrest ACHD

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Perioperative ICU Management of the ACHD Patient by Organ System

Cardiac

Heart Failure

The most common reason for an adult patient with CHD to be admitted to the intensive care unit is heart failure (HF). It is the leading cause of hospitalization, morbidity, and mortality in the adult congenital heart diseases (ACHD) population and is on the rise with annual hospitalizations for ACHD-related heart failure increasing 91% from 1998 to 2011 (Kendsersky et al. 2020; Burchill et al. 2018). While there have been tremendous developments in the management of acquired HF leading to well accepted guidelines and evidence-based therapies, the management of ACHD patients with HF remains ill-defined and murky. This is in part due to the heterogeneity of this population with respect to lesion, anatomy, prior surgical repair, and underlying etiology of the HF.

The presentation of HF in the ACHD patient is highly variable. As such, there is no universally

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accepted definition of heart failure in this population. Patients may present with primarily systolic or diastolic dysfunction, with involvement of either the left, right or single ventricle. Patients who present with left ventricular systolic dysfunction are often those with simple or isolated lesions that have been repaired to normal anatomy. These patients are more likely to benefit from usual medical therapy for HF with afterload reduction, beta blockade, diuretics, and possibly inotropic support for later stage failure. However, patients with more complex disease may present with heart failure without severe decreases in the function of the systemic ventricle and thus the strategy above is less likely to be beneficial. The presence of subpulmonic right ventricular failure is sometimes difficult to identify but may be the primary etiology of failure in some patients, who are also much less likely to benefit from guideline-directed medical therapy. Similarly, patients with a systemic right ventricle or with single ventricle physiology are less likely to respond well to a blanket approach to their HF.

The management of HF in the ACHD patient begins with an investigation to identify and treat any potentially reversible causes that may contribute to heart failure symptoms such as underlying lung disease, new or worsening arrhythmia, acquired shunts, or acquired artero-pulmonary collaterals. Thus, is it recommended that adult patients with CHD who present with HF be referred to an ACHD center with access to interventional radiologists, electrophysiologists, and cardiologists with expertise in the ACHD population.

As far as pharmacologic management of the ACHD patient in acute decompensated heart failure, it is generally believed by most practitioners that inotropic vasoconstrictors such as epinephrine may be less useful in this population as the increased heart rate and myocardial oxygen demand may be poorly tolerated. For patients with right ventricular failure and pulmonary hypertension, medications that lower afterload and promote vasodilation such as milrinone or dobutamine are often beneficial. For the hypotensive patient with low systemic vascular resistance and distributive shock, vasopressin may be favored over norepinephrine as it leads to less vasoconstriction in the pulmonary vascular circulation. A complete list of management considerations by organ system can be seen in Table 1.

For the postoperative ACHD patient presenting with HF, it is imperative to understand the patient's baseline anatomy and physiology, in addition to the surgical procedure performed and its implications. For example, the patient with longstanding insufficiency of the systemic atrioventricular (AV) valve is likely to require inotropic support after repair or replacement of the valve. Knowledge of any intraoperative studies performed including direct hemodynamic and/or pressure measurements during catheterization or surgery is helpful, particularly in the assessment of postoperative volume status which can be difficult in the ACHD patient. Use of invasive pressure monitors including arterial lines, central lines, pulmonary artery catheters, and occasionally left atrial lines should be used. When considering the placement of invasive lines, the individual patient's surgical history and anatomy need to be considered. Patients who have undergone prior classic Blalock–Thomas–Taussig (BTT) shunt, for example, have had alteration of their subclavian artery on one side. As such they likely have lower blood pressure in the affected arm and thus blood pressure monitoring on that side may not accurately reflect central aortic pressure. Thus, ICU physicians must ensure that measured blood pressures correlate with central pressures prior to administering vasoactive medications to treat low blood pressure.

In instances where invasive monitors are not able to be utilized, or for any patient who becomes acutely unstable in the postoperative period, the use of echocardiography should be employed. Echocardiography, both transthoracic (TTE) and transesophageal (TEE), provides valuable information about cardiac output, pulmonary artery pressures, ventricular function, and valvular dysfunction. Additionally, echocardiography may be useful in the evaluation of volume status. It is increasingly being used as a point of care tool in the ICU management of adults with CHD. In addition to direct hemodynamic measurements,

Table 1 Sequelae of CHD

	Sequelae	ICU management considerations
Neurologic	Neurocognitive dysfunction	• Avoid oversedation • Use sedation-agitation-delirium scales
	Prior stroke	• Monitor for stroke • Apply current concepts to minimize risk of delirium
Respiratory	Airway compromise	• Assess for difficult airway management
	Restrictive lung disease	• Avoid PPV if possible • Minimize pressures during PPV • Adjust ventilation to avoid hypoxemia and hypercarbia
	pHTN	• Avoid RV ischemia by maintaining RV coronary perfusion • Avoid sympathetic stimulation, increased intrathoracic pressures, hypercarbia, hypoxemia, acidosis • Avoid pharmacologic increase in PVR
Cardiovascular	Eisenmenger syndrome	• Avoid systemic hypotension • Avoid exacerbation of PVR
	LV dysfunction	• Avoid increased afterload
	RV dysfunction	• Maintain RV coronary perfusion pressure
	Intracardiac shunt	• Air filters on venous access • Avoid increase in right-sided pressures
	Arrhythmias	• Optimize electrolytes; avoid atrial stretch, acidosis, and hypoxemia; minimize sympathetic drive
Hematologic	Anemia	• Knowledge of baseline Hgb level
	Thrombosis	• Anticoagulation • Avoid low-flow states
	Bleeding diathesis	• Optimize coagulation
Renal	Renal dysfunction	• Avoid renally cleared drugs, adjust drug dosing
Hepatic	Congestive hepatopathy	• Minimize fluid load • Maintain right-sided forward flow • Avoid drugs cleared by the liver, adjust drug dosing

pHTN pulmonary hypertension, *LV* left ventricular, *RV* right ventricular, *PVR* pulmonary vascular resistance, *PPV* positive pressure ventilation

Adapted from: Kratzert WB, Boyd EK, Schwarzenberger JC. Management of the Critically Ill Adult With Congenital Heart Disease. J Cardiothorac Vasc Anesth. 2017 Aug;32(4):1682–1700

laboratory values that can be used to assess for the adequacy of systemic perfusion include lactate and central venous oxygenation.

Due to the lack of established evidence-based medical therapies for ACHD patients with HF, mechanical circulatory support is becoming increasingly utilized in this population though patient selection and timing of initiation are still being established (Ross et al. 2016). In 2016 the AHA issued a scientific statement on heart transplantation and MCS in the ACHD patient which includes a framework for when to consider advanced therapies and potential indicators that may help in determining prognosis (Lui et al. 2017). There is no expert recommendation regarding when to refer the ACHD patient with HF for advanced therapies.

MCS in the ACHD Patient

The data regarding outcomes of MCS use in ACHD patients are sparse, especially in the perioperative period (Acheampong et al. 2016). In general, MCS is used far less in the ACHD population than in the acquired heart failure population namely due to more complicated anatomy which makes implantation challenging or even impossible in some cases (Haranal et al. 2020). Furthermore, the presence of comorbidities such as hepatic dysfunction, coagulopathy, protein losing enteropathy (PLE), and chronic infection to name a few, significantly increases the risk of complications associated with MCS. Lastly, lack of experience in this population makes identifying ideal candidates and patient selection chal-

lenging. However, given the limited therapeutic options available for end stage heart in the ACHD patient, the use of MCS in this population is likely to continue increasing and available evidence supports the use of MCS in the ACHD population, thus intensive care providers should be familiar with the unique challenges (Serfas et al. 2018).

Short-Term Support Options

ACHD patients may require short-term mechanical circulatory support postoperatively as a bridge to either recovery, transplant, or durable device (Monaco et al. 2020). Indications for postoperative support include right or left ventricular failure, biventricular failure, persistent arrhythmia, and significant hypoxemia. Options for short-term mechanical circulatory support include extracorporeal membrane oxygenation (ECMO) or a ventricular assist device (VAD). A third option may be use of an intra-aortic balloon pump (IABP); however, unusual anatomy can make placement of an IABP in the ACHD patient impossible. Difficulty with timing of inflation due to persistent arrhythmia poses an additional risk. Lastly, for significant right ventricular failure, or left ventricular failure not associated with coronary artery disease, the IABP is not the preferred modality as these patients often require a higher amount of support. ECMO offers the benefit of providing biventricular support as well as oxygenation for hypoxemia. The most commonly used percutaneous short-term VAD is the Impella (Abiomed, Davers, MA), of which the models available for left ventricular support include the Impella CP, Impella 5.5, Impella 5.0, and the Impella 2.5. For right ventricular failure the Impella RP is available, however, requires the patient to have normal subpulmonic anatomy. Additional percutaneous ventricular assist devices include TandemHeart (CardiacAssist Inc., Pittsburgh, PA) and ProTek Duo (CardiacAssist).

For patients needing biventricular support, veno-arterial ECMO (VA-ECMO) is needed. There are various options for placement of the cannulas which should be decided based on indication for support, patient anatomy, and urgency of cannulation. It is helpful to carefully consider the location for cannula placement prior to surgery, should it be anticipated that a patient may require ECMO in the perioperative period. The presence of artificial conduits and the exact vascular anatomy should be known well in advance of the decision to proceed with MCS. History of difficult venous access due to stenosis or thrombus should be known and venous mapping may be useful in planning. Arterial access can be challenging due to small vessel size, abnormal anatomy, or prior vessel cannulation with injury or repair. A discussion should be had with the perfusionist regarding appropriate cannula size needed to achieve adequate flows (Schweiger et al. 2018). The most common cannulation strategy is in the groin via the femoral vessels for either VV or VA-ECMO; however, consideration can be given to the internal jugular as a site of venous cannulation. Rarely, the axillary artery can also be considered as a site of arterial cannulation. For urgent cannulations in the decompensated patient peripheral cannulation via the femoral vessels is most commonly used as it can generally be accomplished in the shortest amount of time. For postcardiotomy cardiogenic shock, or patients post-cardiac surgery who cannot be weaned from cardiopulmonary bypass, it is possible to use the existing bypass cannulas and leave the chest open with plan to return to the operating room for closure at a later date.

Regardless of the cannulation strategy that is chosen, these short-term MCS options place the patient at risk for a myriad of complications for which the ICU practitioner should be aware. Arterial cannulation can result in vessel occlusion and interruption of blood flow distal to the cannula. Prolonged interruption of flow and ischemia can ultimately result in development of compartment syndrome, thus close monitoring of distal pulses via palpation and doppler is required. Patients requiring MCS are also at increased risk for both thrombus formation and hemorrhage. The European Life Support Organization (ELSO) recommends systemic anticoagulation for patients on ECMO. In the ACHD patients who

may already have impaired liver function and underlying coagulopathy as a result of their congenital heart disease, the risk of bleeding complications is high. Common sites include gastrointestinal bleeding, bleeding around cannula sites, and oropharyngeal or nasal bleeding. In addition to bleeding complications, other significant risks associated with the use of MCS include stroke and infection. Any change in neurologic exam should warrant further evaluation, particularly in the patient with intracardiac shunt at risk for paradoxical embolism. Similarly, practitioners should have a low threshold to workup any sign of potential infection. It is reasonable to initiate broad spectrum antibiotics while awaiting further workup and culture data, as the presence of indwelling catheters and cannulas drastically increases the risk of bacteremia and progression to severe sepsis.

Long-Term Support Options

While there have been tremendous advancements in the realm of left ventricular assist devices (LVAD) for acquired heart failure with approximately 2000 LVADs implanted annually, their use in the ACHD population has been minimal. A 2018 review of the INTERMACs database revealed that only 0.8% of patients with durable VADs were ACHD in 2015. Overall, ACHD patients had higher mortality after implantation than non-ACHD patients; however, this was driven mainly by a larger proportion of ACHD patients who required biventricular support with biventricular assist devices (BiVADs) or total artificial hearts (TAHs) (VanderPluym et al. 2018). It has been proposed that the higher mortality seen in ACHD patients is likely also due to the use of durable MCS as a last resort in patients with end-stage heart failure and multiorgan system dysfunction at the time of implantation. In patients who received an LVAD only, there was no difference in mortality between ACHD and non-ACHD patients, and functional and quality of life measures improved to a similar extent in both groups (Cedars et al. 2018). The results of the review of INTERMACs data are promising and clearly suggest a use and a benefit to using this technology in the ACHD population. In patients with acquired heart failure, outcomes after durable VAD have improved as there has been a trend toward earlier implantation in the more stable patient as opposed to waiting for a decompensation. Thus, it stands to reason that ACHD patients might benefit from a similar strategy.

Some of the unique challenges that have been identified with the use of durable VADs in the ACHD patient include:

- Abnormal ventricular anatomy which is not amenable to standard cannula placement in the apex with the outflow directed toward the aortic valve.
- Extensive trabeculation and moderator band of a systemic right ventricle.
- Multiple prior sternotomies.
- Passive transpulmonary flow, as in Fontan physiology.

Potential solutions to the above challenges have been proposed by Monaco et al. 2020

- Utilization of a nonapical inflow cannula, for example, in the free wall, diaphragmatic surface or atrium.
- Surgical resection of muscle bundles at the time of device implant.
- 3D modeling of relevant anatomy to allow visualization of different device position strategies prior to surgical implantation.
- Increase in device speed until systemic ventricle is fully decompressed to minimize filling pressure.

Arrhythmias

Uncontrolled arrhythmias account for a large proportion of emergency department visits and mortality in the ACHD population. The prevalence and mechanism depend largely on the underlying anatomic defect, prior surgical repair

as well as the current hemodynamics. For example, tachyarrhythmias are seen frequently in the Fontan population and are often poorly tolerated from a hemodynamic standpoint. Furthermore, the presence of sustained tachyarrhythmia can lead to the development of cardiomyopathy and impaired ventricular function. Thus, prompt recognition and intervention to return the patient to a normal sinus rhythm is important. Patients with d-transposition of the great arteries who have undergone a prior Mustard or Senning procedure also frequently develop atrial arrhythmias. Intra-atrial reentrant tachycardia (IART) is particularly common in this population, and is also seen in Fontan patients or after repair of tetralogy of Fallot (TOF).

Management of atrial arrhythmias depends on the clinical stability of the patient. For unstable patients, cardioversion should be performed as soon as possible per ACLS guidelines. For patients who are hemodynamically stable, vagal maneuvers can be tried, followed by adenosine or verapamil. The preferred strategy for long-term management is catheter-based ablation, as this avoids the need for long-term pharmacologic therapy which places the patient at risk for toxicity. While the incidence of amiodarone induced toxicity in the ACHD population is similar to the general population, the incidence of amiodarone-induced thyrotoxicosis in some ACHD patients is higher.

The ACHD patient with persistent atrial arrhythmia is at higher risk for thromboembolic phenomena. Unfortunately, risk scoring systems such as the CHADS2 and CHA2DS2-VASc do not appear to correlate well with actual thromboembolic risk in these patients as they typically have low scores but remain at high risk for events. As such, ACHD patients with atrial fibrillation or flutter are typically anticoagulated regardless of their calculated CHADS2 or CHA2DS2-VASc score.

In ACHD patients who have developed bradyarrhythmias as a result of prior surgical repair, the most likely etiology is due to dysfunction of the sinus node or abnormal atrioventricular conduction. As such, these patients likely have a permanent pacemaker in place. Physicians caring for these patients perioperatively should thus be aware of the patient's baseline rhythm, pacemaker settings, and pacemaker dependency. Changes to these settings may be warranted in the perioperative period to improve cardiac output and thus consultation with electrophysiologists is recommended. For the ACHD patient who develops arrhythmia in the perioperative period, anti-arrhythmics such as amiodarone may be utilized in the short-term for either rhythm or rate control.

Cardiac Arrest and ECPR

In the event of a cardiac arrest, it is of utmost importance to determine the etiology of the decompensation and work to address the underlying problem. The most common etiology for out of hospital cardiac arrest in the ACHD patient is ventricular arrhythmias, with ischemia or infarction being much less common (Vehmeijer et al. 2019). It should be mentioned that especially in young adults with CHD, an important cause of acute coronary syndrome may be abnormal coronary anatomy which leads to myocardial ischemia, particularly with exercise. In the patient who is post-procedure, consideration should also be given to hemorrhage, tamponade, acute thromboembolism, and hypoxia. There are no specific recommendations or guidelines for the management of cardiac arrest in the ACHD patient. The location of chest compressions may need to be adjusted depending on the patient's anatomy. Similarly, it is important to allow for full chest recoil during compressions in order to allow blood to flow forward through the pulmonary vasculature in patients with Fontan physiology. ACLS algorithms should be followed while giving early consideration to the potential need for mechanical circulatory support (Link, et al. 2015). Especially if the factors contributing to the arrest are thought to be reversible, MCS can be used as a bridge to recovery. For the ACHD patient who arrested due to decompensated HF, MCS can be a bridge to durable therapy or transplantation. Occasionally, it may be necessary to use MCS as a bridge to decision to determine

transplantation or durable therapy candidacy. In the postoperative patient who arrests, the cardiac surgery advanced life support (CALS) guidelines should be considered with emphasis on early defibrillation, pacing if temporary epicardial wires are available, and early resternotomy.

Extracorporeal cardiopulmonary resuscitation (ECPR) refers to the implantation of veno-arterial extracorporeal membrane oxygenation (VA-ECMO) in a patient who experienced a sudden and unexpected pulseless condition attributable to cessation of cardiac mechanical activity (Pappalardo et al. 2017). The use of ECPR requires experienced practitioners capable of establishing adequate vascular access, as well as specialized equipment. ECPR is now recognized by ELSO and the American Heart Association as a technique that can be considered in select patients who suffer from a cardiac arrest. In fact, the most recent 2015 AHA guidelines on adult ACLS now include ECPR as a consideration.

While there are no studies to date on the use of ECPR in the ACHD population specifically, these patients may suffer from the same reversible causes of cardiac arrest for which ECPR should be considered. These include acute coronary artery occlusion, pulmonary embolism, refractory ventricular fibrillation (VF), cardiac injury, myocarditis, cardiomyopathy, congestive heart failure, or drug intoxication. For a list of the inclusion and exclusion criteria from some of the key ECPR articles, we direct readers to the 2015 AHA ACLS guidelines. When faced with an ACHD patient in cardiac arrest, particularly in the perioperative period, it is reasonable to consider the use of ECPR. Should the decision be made to proceed with ECPR, practitioners should continue to utilize the ACLS algorithm during cannulation. It is critical that high quality chest compressions be continued and that interruption in chest compressions be kept to a minimum.

Neurologic

Neurologic sequelae of congenital heart disease include stroke, seizures, abnormal neurocognitive development, and psychiatric disorders. The risk for stroke is especially high in this population as compared to the general population (Gaeta et al. 2016). Ischemic strokes can occur in older patients; however, other causes including thromboembolic sources should also be on the differential. An important consideration for the ICU practitioner is the increased risk for paradoxical embolization of air or thrombus due to the presence of intracardiac shunts. Conditions that increase right sided pressures such as significant tricuspid regurgitation and positive pressure ventilation may further increase the risk. Careful administration of intravenous medications and use of air filters is essential and long-term indwelling lines should be avoided if possible. Any abnormal finding on neurologic evaluation that is a change from the patient's baseline should be promptly and thoroughly evaluated.

Seizures may be related to structural abnormalities of the brain, or associated with underlying congenital syndromes. Additionally, neurocognitive development may be impaired in patients with CHD owing to chronic hypoxemia, abnormal cerebral vasculature, and exposure to cardiopulmonary bypass, hypothermic circulatory arrest and anesthesia as a result of frequent surgeries early in life. As a result, cognitive, motor, and language impairments are frequently seen in these patients. Furthermore, the frequent need for surgery, hospitalization, and stays in the intensive care unit may contribute to the development of psychological and psychiatric disorders including anxiety, depression, and even post-traumatic stress disorder. A thorough review of home medications is warranted on admission to the ICU. Home antidepressant and anxiolytic medications should typically be continued if it safe to do so, the ICU physician should have an awareness of potential drug interactions and if the risk of interaction and oversedation is significant, home medications should be held.

Careful attention should be paid to the management of pain in the ACHD patient. Given that up to one-third of ACHD patients have pulmonary hypertension, it is important to consider the effects of pain, but also hypercapnia, hypoxemia, and acidemia on the pulmonary vascular resistance. Use of multimodal pain regimens that

employ regional anesthetic and opioid sparing techniques is recommended to avoid the side effects of oversedation and hypoventilation that often accompany opioid medications.

When sedation is necessary, there are several options available. Benzodiazepines, opioids, and propofol can all be safely administered; however, the increased risk for ICU delirium and potential for withdrawal with prolonged use of benzodiazepines should be noted. Dexmedetomidine may be preferred as its use is not associated with significant respiratory depression and its effects on heart rate may be beneficial in the patient who is prone to tachyarrhythmias. Practitioners should be mindful however that the decrease in heart rate may be associated with a significant drop in cardiac output which may be poorly tolerated and may limit its use in some patients. In agreement with current standards of care and ICU guidelines for the management of sedation in all patients, deep sedation should be avoided whenever possible and sedation scales should be utilized with specific targets for titration of medications. The ACHD patient may be particularly prone to the adverse physiologic effects of oversedation which include respiratory acidosis, arrhythmia, hemodynamic instability, and delirium. Evidence-based strategies for the prevention of delirium should be employed, including early mobilization, normalization of sleep/wake cycles, and avoidance of benzodiazepines.

Pulmonary

Pulmonary pathology is frequently seen in ACHD patients. Restrictive lung disease has a prevalence of nearly 50% in ACHD patients, and is particularly common in tetralogy of Fallot and Fontan patients. Restriction may result from external forces exerted on the chest wall such as scoliosis, multiple prior sternotomies, and muscle weakness. Or may be the result of internal forces including chronic inflammation and alterations in the pulmonary vasculature. Pulmonary hypertension is common in the ACHD population and warrants consideration. Pulmonary hypertension is a broad term that includes pulmonary arterial hypertension and pulmonary venous hypertension (Stout et al. 2018). In the ACHD patient, elevated pulmonary pressures may result from a longstanding unrestricted left-to-right shunt, a failing systemic ventricle, severe stenosis or regurgitation of the systemic atrioventricular valve, or pulmonary thromboembolic disease. Classic teaching includes the avoidance of hypothermia, metabolic acidosis, hypercarbia, and hypovolemia which can all increase the pulmonary vascular resistance (PVR). Knowledge of the patient's baseline pulmonary vascular pressures and PVR can be useful when deciding whether the use of pulmonary vasodilators may be necessary. The most commonly used pulmonary vasodilator used in the ICU is inhaled nitric oxide (iNO). Nitric oxide works by increasing levels of cyclic guanosine monophosphate (GMP) in smooth muscle cells of the lung. It has a short half-life which is beneficial in the critical care setting. The inhalational route of administration is advantageous as the vasodilatory effects are localized to the pulmonary vasculature without a simultaneous drop in the systemic vascular resistance. Downsides to the use of iNO include tachyphylaxis as well as the development of methemoglobinemia, the development of which patients should be closely monitored for. As an alternative to iNO, inhaled prostacyclin analogues including epoprostenol, treprostinil, and iloprost can also be used. These medications have longer half-lives and do not require continuous nebulization. Lastly, the phosphodiesterase-5 inhibitor sildenafil can also be considered as it also results in selective vasodilation in the pulmonary vasculature. It is more easily administered as it is available in oral preparation; however, caution should be used when initiating as it can lead to profound systemic hypotension. Thus, practitioners should consider using the lowest dose possible to start and slowly titrating to the desired effect.

Hypoxemic respiratory failure postoperatively or post-procedurally may be due to a variety of causes. In patients with a stenotic pulmonic valve who have undergone dilation or replacement, relief of the obstruction or stenosis results in a significant increase in blood flow and has the

potential for acute lung injury and pulmonary edema as a result of reperfusion. In fact, for any patient with significant pulmonary hypertension, the sudden and dramatic increase in pulmonary blood flow as might occur when separating from cardiopulmonary bypass can also result in a similar type of reperfusion injury with edema. If this occurs, management may include diuresis and lung protective ventilation to allow for recovery of the injured lungs without causing further injury. Rarely, severe edema and hypoxemia may necessitate use of MCS in order to allow for lung recovery.

The need for intubation in the ACHD patient should be accompanied by a thorough review of the current anatomy/physiology as well as a detailed airway history with respect to any prior reports of difficult intubation, tracheal stenosis or stricture, prior tracheostomy, etc. Whenever possible, intubation should be avoided in ACHD patients with significant pulmonary hypertension (PH) or Fontan physiology because the sudden introduction of positive pressure ventilation can lead to a significant drop in preload and systemic hypotension with instability. If intubation is required, providers should ensure adequate intravascular volume and may even consider administration of a volume bolus prior to intubation. Mechanical ventilation settings should include use of low positive end-expiratory pressure (PEEP) and lower tidal volumes of no more than 6–8 cc/kg. For the patient who was intubated peri-procedurally, ICU providers should move toward extubation as soon as is safe. Patients with certain complex lesions such as heterotaxy syndrome may have ciliary dysfunction and dysmotility that results in an increased risk of prolonged ventilation and ventilator associated pneumonia. Consideration can be given to extubating to noninvasive positive pressure (Weismann et al. 2012).

Gastrointestinal and Hepatic

Hepatic dysfunction in the ACHD patient is typically a consequence of chronically elevated central venous pressures which are transmitted back into the hepatic system resulting in hepatic congestion, inflammation, fibrosis, and ultimately cirrhosis (Lei Lei et al. 2021). Patients at risk for development of this so-called cardiac cirrhosis include those with a Fontan and single-ventricle circulation, Ebstein's anomaly, repaired tetralogy of Fallot with pulmonary insufficiency, or severe tricuspid regurgitation. A second important cause of hepatic dysfunction in ACHD patients is hepatitis C infection from prior blood transfusion. Patients who underwent cardiac surgery prior to the 1990s when universal screening of blood products began are at risk for having contracted hepatitis C. Preoperative risk stratification is challenging as laboratory live function tests, imaging, and degree of liver impairment do not often correlate well with one another. The Model for End-stage Liver Disease eXcluding INR (MELD-XI) may be helpful as it has been shown to be a predictor of MACE in ACHD patients.

Consequences of liver failure in these patients include hematologic abnormalities resulting in increased need for transfusion and protein losing enteropathy (PLE). PLE involves a loss of integrity of the lining of the gastrointestinal tract, which results in protein loss in the stool. This results in hypoalbuminemia and low intravascular oncotic pressure which may ultimately lead to ascites, pleural effusions, malnutrition, and impairment in immune function. ICU management of these patients in the perioperative period should include a plan for optimizing nutritional status.

Renal

Renal dysfunction is associated with a notable increase in morbidity and mortality in the ACHD population (Dimopoulos et al. 2008). Patients with mild renal insufficiency are at two times the risk of mortality over 6 years, and those with moderate to severe renal insufficiency are at five times the risk. Cyanotic heart lesions which result in hyperviscosity seem to lead to more significant renal impairment. In addition, surgical and catheter interventions place these patients are high risk for acute on chronic kidney injury in the peri-

operative period. Exposure to nephrotoxic agents including intravenous iodinated contrast and prolonged cardiopulmonary bypass runs should alert the ICU physician to the need for close monitoring of renal function. Avoidance of nephrotoxic agents and careful dosing of medications in the presence of any renal dysfunction are important parts of perioperative management of ACHD patients.

Patients with CHD are also at risk for developing cardiorenal syndrome (CRS). Type I (acute) cardiorenal syndrome can be thought of as acute heart failure which leads to acute kidney injury. In contrast, type II (chronic) occurs when chronic heart failure results in chronic kidney disease (CKD) (Janani et al. 2019). In either case, development of CRS makes management of underlying heart failure more difficult, particularly with respect to volume management. Use of renal replacement therapies such as continuous renal replacement therapy (CRRT) or SLED (sustained low-efficiency dialysis) can be used; however, it is most important to identify and address the underlying etiology of the renal failure. Development of renal failure and need for long-term renal replacement complicates long-term management of these patients as it may sometimes preclude them from transplant candidacy. The decision to initiate renal replacement therapy should be made by the ICU physician in consultation with nephrology and cardiology. Vascular access may again pose a problem and thus consideration should be given to involving Interventional Radiology to assist with placing dialysis catheters under fluoroscopic guidance if needed.

Hematologic

Hematologic abnormalities seen in the ACHD population include anemia, erythrocytosis, thrombocytopenia, thrombosis, as well as factor deficiencies. Patients with longstanding cyanotic lesions including Eisenmenger syndrome often develop erythrocytosis, whereas patients with elevated central venous pressures as in the case of Fontan physiology often have factor deficiencies as a result of hepatic dysfunction. In patients who have recently undergone a procedure, the most common cause of anemia is acute blood loss. It is possible for these patients to have ongoing blood loss in the ICU; therefore, it is of the utmost importance to be vigilant with postoperative monitoring. Close attention should be paid to drainage from any indwelling tubes such as pleural or mediastinal tubes and this should be trended over time. In the absence of ongoing blood loss, it is reasonable to undertake a workup for other causes of persistent anemia. Iron studies to evaluate for iron deficiency and indicators of hemolysis such as LD, haptoglobin, and plasma-free hemoglobin may be considered.

ACHD patients can be at increased risk for hemorrhagic complications as well as thrombosis. Increased risk of hemorrhage is seen in patients with thrombocytopenia, factor deficiencies due to underlying liver disease and those who are chronically anticoagulated. It is a careful balance in the ACHD patient to correct coagulopathy in the presence of ongoing bleeding, while also being mindful of the risks of transfusion including allosensitization which may affect a patient's transplantation candidacy in the future.

An increased risk of thrombosis may be seen in patients with secondary erythrocytosis and hyperviscosity. In the postoperative and post-procedure patient, indwelling central lines, inflammation, and/or coagulopathy secondary to extracorporeal circulation can all increase the risk of thrombus formation. Should a venous thromboembolism (VTE) be diagnosed, treatment should be initiated as soon as possible. Unfractionated heparin or low-molecular weight heparin may be used and titrated to a target anti-factor Xa level of 0.3–0.7. While hospitalized, we recommend use of short acting and easily reversible agents. When patients are ready for discharge, they can be transitioned to warfarin for long term therapy.

Infectious Disease

Compared to the general population, patients with congenital heart disease have an increased

risk of complications from infectious diseases. ICU practitioners should be aware of the increased risk for infective endocarditis (IE) in the ACHD patient. Prior data suggests that ACHD patients may have as much as a 20–40 times higher incidence of IE than the general population. Presence of prosthetic material, recent dental work, low-flow states, and surgical or interventional procedures greatly increase this risk. Practitioners should consider each individual patient's risk, and be familiar with general IE guidelines regarding antibiotic prophylaxis and therapy. Consultation with an infectious disease specialist may be warranted. Given that IE represents a significant contributor to mortality in the ACHD population, prompt recognition, evaluation, and initiation of treatment are critical.

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Nutritional Supports in Congenital Heart Disease

Mahdi Shadnoush and Vahid Maleki

Abstract

Malnutrition is one of the known congenital heart disease (CHD) consequences that gets worsen by heart failure, malabsorption, hypermetabolism, and inadequate intake of required nutrients. Optimal nutritional support is essential for post-operational recovery, reduction of infection, and mortality in patients with CHD. While there are wide options in the management of nutritional support for CHD worldwide, several concerns stand for the potential risk of complications related to the type of nutrition support (oral, intestinal, intravenous, and trophic), precise timing, and reasons for not achieving goals such as nutritional intolerance, malabsorption, and hypermetabolism. Further complications include chylothorax, necrotizing enterocolitis, cyanosis or hypoxemia or ductal dependent systemic circulation, heart failure, fluid restriction, malabsorption, hypoperfusion intestinal, and laryngeal dysfunction can challenge nutritional support. The main aim of this study is to summarize recent findings and present a practical model and standard protocol for the principles of nutritional support and challenges in patients with CHD.

Keywords

Nutritional support · Malnutrition · Malabsorption · Resting energy expenditure · Necrotizing enterocolitis · Chylothorax · Prostaglandin E1 · Extracellular membrane oxygenation · Congenital heart disease · CHD

Introduction

Congenital heart disease (CHD) is still the most common congenital disability, with an approximate birth rate of 5–11 per 1000 live births and a 1% incidence (Van Der Bom et al. 2011; Bouma and Mulder 2017). Malnutrition is the most critical and common problem with congenital heart disease (CHD), especially in infants and children (Tabib et al. 2019). Disease-related malnutrition can lead to increased infection, delayed recovery, prolonged hospital stay, prolonged ventilation, poorer growth outcomes, and higher rate of mortality (Meyer and Valentini 2019; Vaidyanathan et al. 2008). Therefore, initiation of nutritional support and adequate intake of nutrients and

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energy will prevent the consequences of malnutrition (Toole et al. 2014; Hubschman 2013).

Malnutrition refers to a diet with deficient, or imbalance intake of energy or nutrients which in case of CHD specifically refers to imbalance energy intake that is mainly due to anorexia, reflux, dysphagia, malabsorption, increased energy consumption due to catabolic stress due to disease caused by increased cardiac and pulmonary load, chronic hypoxia, and metabolic stress (Hubschman 2013; Hagau and Culcitchi 2010). The development of malnutrition in CHD patients leads to myocardial dysfunction, vascular endothelial dysfunction, skeletal muscle atrophy, immunosuppression, and increased insulin resistance and lipolysis (Zhang et al. 2020; Murni et al. 2017). Therefore, early nutritional support can increase the recovery process and reduce complications and mortality (Ross et al. 2017; Fitria et al. 2019). In addition, in a short phase following surgery, increase in metabolic stress under inflammatory responses induction, leads to a significant temporary increase in resting energy consumption and protein catabolism (Silva-Gburek et al. 2019; Cabrera et al. 2010).

Since nutritional status considered as a potential but modifiable risk factor, optimizing preoperative nutritional status can improve short-term and long-term outcomes. This study aimed to evaluate various aspects of nutritional support in patients with CHD before, during, and after surgery on clinical outcomes.

Types of Congenital Heart Defects

Congenital heart defects classified based on anatomy and pathophysiology as follows: (Van Der Bom et al. 2011) CHD with a shunt between systemic and pulmonary circulation, (Bouma and Mulder 2017) CHD of the left heart, (Tabib et al. 2019) CHD of the right heart, (Meyer and Valentini 2019) CHD with the abnormal origin of large vessels, and (Vaidyanathan et al. 2008) Miscellanea (Kantor and Redington 2010; Thiene and Frescura 2010). In general, the main features of CHD include (Van Der Bom et al. 2011) the presence of shunts between arterial and venous blood, (Bouma and Mulder 2017) cyanosis, and (Tabib et al. 2019) changes in the circulatory system (Moussa et al. 2017). A shunt involves an abnormal path between two chambers of the heart or arteries through which blood flows from one side to the other, that may be left-to-right, right-to-left, or bilateral, and the direction of blood flow through a pressure gradient across (Beghetti and Tissot 2010; Sommer et al. 2008). The shunt depends on where the blood usually flows from the left heart (high pressure) to the right heart (low pressure). Therefore, the direction of shunting can affect its function by affecting the condition of pulmonary blood flow. In the large left-to-right (LR) shunt, blood flow to the lungs increases, leading to shortness of breath and vascular bulge (Barua et al. 2015).

Finally, left ventricular volume (LV) overload with ventricular dilatation and subsequent heart failure (Sakata et al. 2013; Aburawi and Pesonen 2011), and pulmonary artery pressure overload, which leads to increased pulmonary blood pressure (PH), increased pulmonary vascular resistance (PVR), and obstructive pulmonary vascular disease (PVOD) (Koestenberger et al. 2012; Micheletti 2019). In contrast, in the right-to-left shunt, venous blood flow (containing low oxygen) mixes with arterial blood flow (high oxygen). It causes cyanosis, which appears as a bluish discoloration on the skin and mucous membranes (Micheletti 2019; Jamei et al. 2017; Ketut Alit Utamayasa et al. 2020).

Effects, Challenges, and Side Effects of CHD

Hypermetabolism

Total energy expenditure (TEE), the sum of all energy consumed in a day, includes resting energy expenditure (REE), thermogenic food effects, physical activity, and required energy for synthesizing new tissues (Maleki et al. 2017). The amount of energy necessary to maintain energy balance in a healthy person with a specific age, sex, weight, height, and level of physical

activity. (The following formula indicates the energy balance conditions) (Hill et al. 2012).

$$E_{\text{intake}} - E_{\text{feces}} - E_{\text{urine}} - E_{\text{combustible gas}} - E_{\text{expenditure}} = E_{\text{retention}} \text{ or } E_{\text{secretion}}$$

Infants, children, adolescents, and pregnant or lactating women required enough energy for tissue deposition, repair, and milk production while maintaining good health (Butte and King 2005; Torun 2005). Basal metabolic rate (BMR) in infants is between 43 and 60 kcal/kg body weight per day, which is 2–3 times higher than adults (Butte 2005). The need for energy decreases with aging means that the required energy for growth reduces from 35% in a 1-month infant to 3% at 12 months and reaches again by 4% during adolescents (Torun 2005; Butte 2008).

According to the dietary reference intakes (DRIs), the amount of required energy from 0 to 3 months is 175 kcal per day, 60 kcal per day for 4–6 months, and 20 kcal per day for 7–35 months is estimated (Nutrition SACo 2012). In healthy adults who are at a constant weight, required energy is equal to their total energy expenditure (TEE), however in patients, which disease-induced stress energy expenditure may increase substantially (Intakes IoMSCotSEoDR 1997; Ndahimana and Kim 2018). On the other hand, the doubled-labeled water method to calculate TEE and indirect calorimetry (IC) to measure REE are more accurate (Johannsen et al. 2010).

Indirect calorimetry (IC) calculates heat production by measuring the patient's lung gas exchange rate. In this method, REE is determined using oxygen consumption, carbon dioxide production, and the amount respiration rate (RQ) (Mtaweh et al. 2018).

If IC is not available, standard equations (WHO, Harris-Benedict, and Schofield equations) can be used (Alfonzo-González et al. 2004; Subramaniam et al. 2012). These predictive equations are less reliable because they do not involve changes in body mass, sedative use, paralysis, or other stressors that a greater risk of using equations for overeating and malnutrition (Kamiyama et al. 2016; Frankenfield et al. 2005).

TEE in patients with CHD before surgery increases due to increased metabolic load such as increased respiratory work, increased cardiac output, high pulmonary artery pressure, and excessive secretion of catecholamines (Trabulsi et al. 2015). Also, after surgery, a severe inflammatory response leads to an increase in resting energy intake (REE) in patients with CHD, resulting in increased postoperative caloric needs (Nydegger et al. 2009; Xie et al. 2017). However, this rate is variable and not easily predictable because the catabolic stress response varies significantly from patient to patient and to factors such as the duration and severity of the injury or disease, the complications of the disease, therapeutic interventions, and respiratory support depends (De Wit et al. 2010). Also, preoperative malnutrition can increase the intensity of basal metabolism and protein catabolism. Therefore, nutritional support before and after surgery can reduce the complications of surgery and mortality by accurately determining the need for energy (Toole et al. 2014; Wong et al. 2015).

Nutritional Support in Patients with CHD

Calorie Requirements

Ideally, indirect calorimetry (IC) should be used to estimate energy needs in the patients (De Wit et al. 2010; Roebuck et al. 2020). In this method, oxygen consumption is an essential component in determining energy intake that can be used serially to monitor changes in a patient's clinical condition for accurate estimate of need energy in these patients (Roebuck et al. 2020). In the case of blood gas levels change the using of IC to estimate energy is not reliable, such as people in need of high-pressure oxygen or supplemental oxygen, acidosis, air leakage from endotracheal tubes, high or unstable FiO_2, and hemodialysis (Mtaweh et al. 2018; McClave et al. 2013).

In patients with CHD, resting energy expenditure (REE) after surgery is often increased due to increased metabolic stress and inflammation, and

calorie requirements vary from patient to patient and depend on age, sex, weight, preoperative nutritional status, duration, and severity of the disease (Trabulsi et al. 2015; Xie et al. 2017). There is currently debate to determine what weight should be used in energy calculation formulas in estimation formulas (Krenitsky 2005; Psota and Chen 2013). However, in the absence of indirect calorimetry, the standard equations in Tables 1 and 2 can be used.

Table 1 Common predictive equations for calculating resting energy expenditure

Formula	Age (years)	Equation	
		Male	Female
WHO (1985)	0–3	$(60.9 \cdot W_{kg}) - 54$	$(61.0 \cdot W_{kg}) - 51$
	3–10	$(22.7 \cdot W_{kg}) + 495$	$(22.5 \cdot W_{kg}) + 499$
	10–18	$(17.5 \cdot W_{kg}) + 651$	$(12.2 \cdot W_{kg}) + 746$
Schofield (1985)	0–3	$(0.167 \cdot W_{kg}) + (15.174 \cdot H_{cm}) - 617.6$	$(16.252 \cdot W_{kg}) + (10.232 \cdot H_{cm}) - 413.5$
	3–10	$(19.59 \cdot W_{kg}) + (1.303 \cdot H_{cm}) + 414.9$	$(16.969 \cdot W_{kg}) + (1.618 \cdot H_{cm}) + 371.2$
	10–18	$(16.25 \cdot W_{kg}) + (1.372 \cdot H_{cm}) + 515.5$	$(8.365 \cdot W_{kg}) + (4.655 \cdot H_{cm}) + 200.0$

Table 2 Energy requirement for healthy children, FAO/WHO/UUN Joint Commission[a] (FAO 2004)

Infant					Toddler and adolescent				
Age	Sex	Total energy expenditure[b,c]	Energy deposited in tissue	Daily energy requirement	Age	Sex	Total energy expenditure[b,c,d,e]	Energy deposited in tissue	Daily energy requirement
0–1 month	Male	66.8	46.1	113	1–2 years	Male	81.2	1.2	82
	Female	65.7	40.9	107		Female	78.8	1.3	80
1–2 months	Male	70.5	33.3	104	2–3 years	Male	82.7	0.8	84
	Female	69.3	31.3	101		Female	79.6	0.9	81
2–3 months	Male	72.8	22.1	95	3–4 years	Male	79.0	0.8	80
	Female	71.5	23.0	95		Female	75.8	0.7	77
3–4 months	Male	74.2	7.6	82	4–5 years	Male	76.2	0.6	77
	Female	73.2	10.6	84		Female	73.3	0.6	74
4–5 months	Male	75.3	6.0	81	5–6 years	Male	73.9	0.6	74
	Female	74.3	8.2	83		Female	71.0	0.5	72
5–6 months	Male	76.0	4.5	81	6–7 years	Male	71.9	0.6	72
	Female	75.1	6.4	81		Female	68.7	0.6	69
6–7 months	Male	76.6	2.0	79	7–8 years	Male	70.0	0.6	71
	Female	75.7	2.6	78		Female	66.0	0.7	67
7–8 months	Male	77.0	1.9	79	8–9 years	Male	67.9	0.6	69
	Female	76.2	2.1	78		Female	63.1	0.8	64
8–9 months	Male	77.4	1.6	79	9–10 years	Male	66.0	0.6	67
	Female	76.7	1.8	78		Female	60.0	0.8	61
9–10 months	Male	77.8	2.3	80	10–11 years	Male	63.9	0.7	65
	Female	77.0	2.1	79		Female	57.1	0.7	58
10–11 months	Male	78.0	2.2	80	11–12 years	Male	61.8	0.7	62
	Female	77.3	1.7	79		Female	54.2	0.6	55
11–12 months	Male	78.3	2.3	81	12–13 years	Male	59.5	0.7	60
	Female	77.6	1.6	79		Female	51.4	0.6	52

(continued)

Table 2 (continued)

Infant					Toddler and adolescent				
Age	Sex	Total energy expenditure[b,c]	Energy deposited in tissue	Daily energy requirement	Age	Sex	Total energy expenditure[b,c,d,e]	Energy deposited in tissue	Daily energy requirement
					13–14 years	Male	57.3	0.7	58
						Female	48.8	0.5	49
					14–15 years	Male	55.0	0.6	56
						Female	46.6	0.4	47
					15–16 years	Male	52.9	0.5	53
						Female	45.1	0.2	45
					16–17 years	Male	51.2	0.4	52
						Female	44.3	0.1	44
					17–18 years	Male	50.1	0.2	50
						Female	44.1	0	44

[a]Adapted from Joint FAO/WHO/UUN Expert Consultation, human energy requirements
[b]TEE, male, 0–12 months, $-99.4 + (88.6 \cdot W_{kg})$
[c]TEE, male, 1–18 years, $310.2 + (63.3 \cdot W_{kg}) - (0.263 \cdot W_{kg^2})$
[d]TEE, female, 0–12 months, $-99.4 + (88.6 \cdot W_{kg})$
[e]TEE, female, 1–18 years $263.4 + (65.3 \cdot W_{kg}) - (0.454 \cdot W_{kg^2})$

Preoperative Nutritional Support

Methods of preoperative nutritional support are heterogeneous worldwide, and there is no set strategy for starting feedings (Toole et al. 2014; Radman et al. 2014). Main goals of nutritional support in preoperative are to improve the growth, immune system, and health of the intestinal mucosa (Toole et al. 2014; Kataria-Hale et al. 2021a). Differences in nutritional support practices and disagreements about optimal preoperative nutritional support may lead to poor growth in the postoperative period (Toole et al. 2014; Wong et al. 2015). Studies show that poor preoperative nutrition in a patient with CHD is associated with poor clinical outcomes (Toole et al. 2014). This is a concern because poor nutritional status and low weight during surgery may lead to increased mortality (Larsen et al. 2013; Eskedal et al. 2008; Mitting et al. 2015). However, there are concerns about the onset of nutritional support in the preoperative period due to complications such as systemic perfusion, necrotizing enterocolitis (NEC), and intestinal ischemia (Morgan et al. 2013; Tsintoni et al. 2020).

Studies support the beneficial role of preoperative nutrition. In general, nutritional support preoperative leads to a reduction in the duration of mechanical ventilation, more stable postoperative hemodynamics, better feeding tolerance and wound healing, reduced mechanical ventilation time, a decrease in infection, fluid overload, and length of hospital stay in the postoperative phase (Wong et al. 2015; Zyblewski et al. 2015; Kataria-Hale et al. 2021b). In this regard, several CHD care institutions have published nutrition support protocols (Kataria-Hale et al. 2021a; Slicker et al. 2016; Marino et al. 2018; del Castillo et al. 2010; Tume et al. 2018; Gephart et al. 2018). However, the results contradict enteral nutrition (EN), and there are concerns before the surgery. Despite little evidence of intestinal perfusion about starting EN preoperative due to concerns about the complication, physicians usually discontinue bowel therapy in receiving the patient from prostaglandin E1 (PGE1) (Lewis et al. 1981). In this regard, studies have shown contradictory results. Howley et al. reported in prostaglandin-dependent infants, 56% of patients in the United States and 9% in other regions did not receive EN (Howley et al. 2012). In contrast, Toms et al. reported no cases of NEC in a group of hypoplastic left heart syndrome (HLHS) patients receiving low-volume diets (Toms et al. 2015). Natarajan et al. reported infant feeding with PGE1 was well tolerated when receipt of 100 mL/kg was obtained in 75% of patients and complete nutrition in 29% of neonates (Natarajan et al. 2010). However, the nutrition of prostaglandin-dependent infants remains controversial and unclear (Willis et al. 2008). It seems that prostaglandin-dependent intestinal nutrition is safe in some cases and can be started in those who are hemodynamically stable (Medoff-Cooper and Ravishankar 2013). The European Society for Child and Neonatal Intensive Care (ESPNIC) recommends that nutritional support can be started in patients with stable hemodynamic status with or without cardiovascular drug support within the first 24 h (Tume et al. 2020).

As a whole, the available evidence suggests that EN can be performed with evaluation and monitoring in patients with hemodynamic stability. However, parenteral nutrition (PN) support is needed in infants with CHD to meet goals (Martini et al. 2021).

EN starts from 20–25 mL/kg per day and increases to 20 mL/kg/day and reaches the goal of 120–150 mL/kg per day (Tume et al. 2018; Martini et al. 2021). In infants, breast milk is the preferred food if a standard formula is an acceptable alternative (Kataria-Hale et al. 2021a). However, in some patients, poor systemic perfusion or poor cardiac output can lead to nutritional intolerance (Slicker et al. 2013; Typpo et al. 2015).

A recent study showed that using parenteral nutrition (PN) before surgery for 7 days reduces ventilator dependence, infection, and the need for dialysis (Fivez et al. 2015). The effect of total parenteral nutrition (TPN) in the preoperative period is not clear exactly whether the benefits outweigh the side effects and whether delays in injectable feeding lead to reduced growth in infants with CHD (LiYing et al. 2017). Studies show that the implementation of feeding proto-

cols based on breastfeeding can improve nutritional status and reduce NEC (del Castillo et al. 2010; Braudis et al. 2009). Mehta et al., in a randomized trial in children with CHD, showed that non-performing TPN compared to early TPN reduced infection and reduced clinical outcomes (Fivez et al. 2016).

Therefore, the risks and benefits of PN should be considered before performing, and designing a protocol for assessing and predicting the risks of implementing pre- and postoperative nutritional support in patients with CHD can be prevented (Fig. 1).

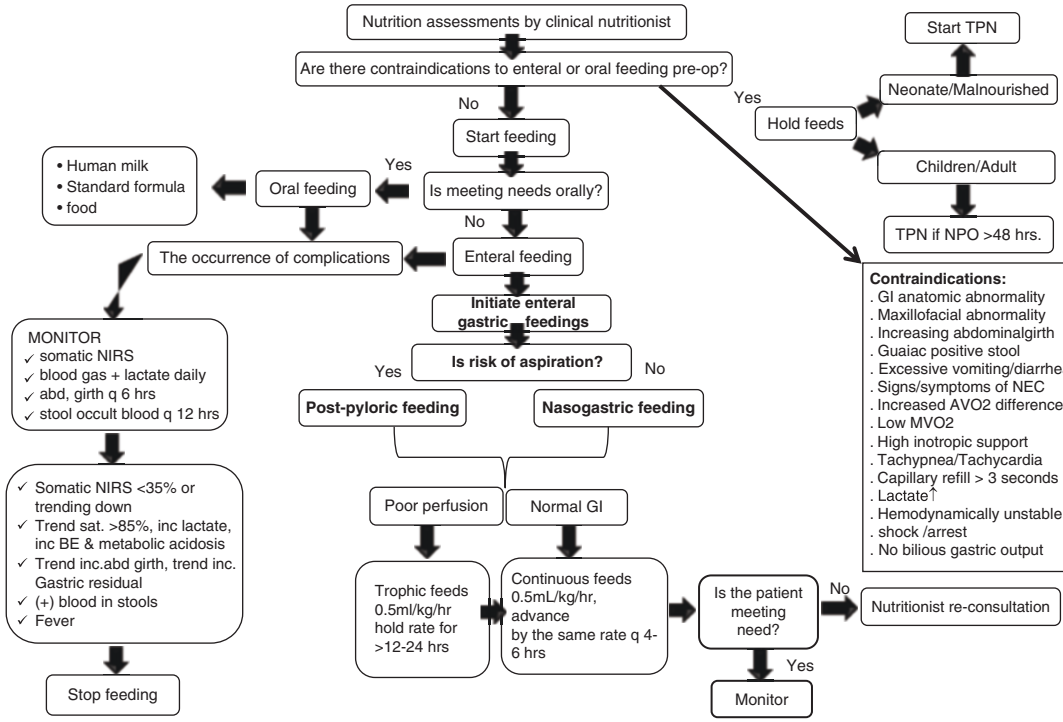

Fig. 1 Flowchart of the feeding process preoperative and postoperative surgery in congenital heart disease

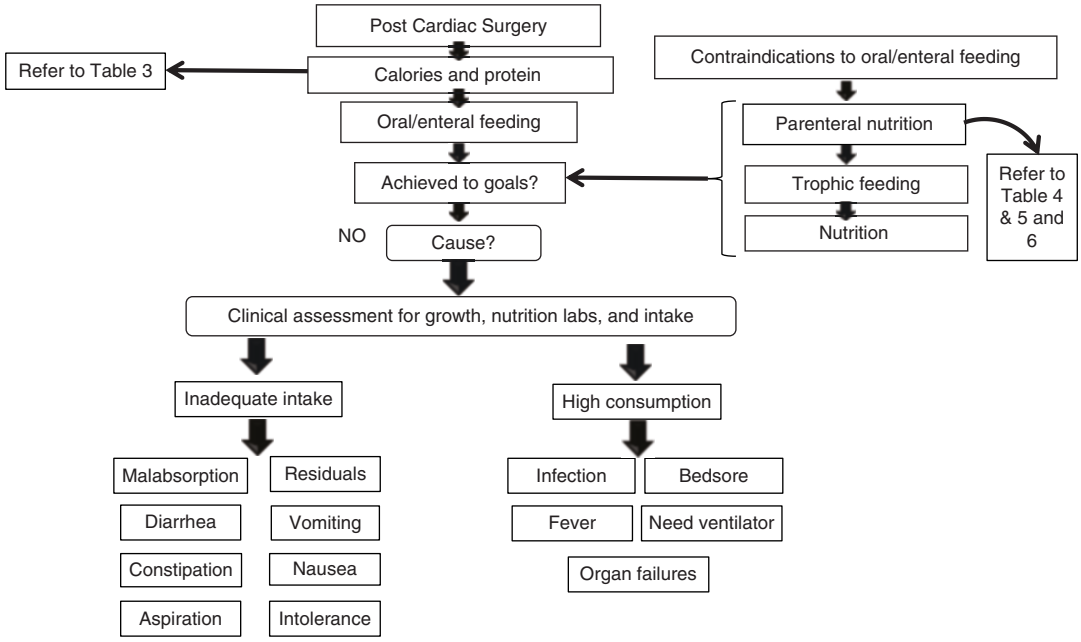

Fig. 1 (continued)

Postoperative Nutritional Support

Early initiation of nutritional support with EN, PN, and combination therapies can reduce complications, length of stay, and mortality in patients with CHD after surgery (Boctor et al. 1999). Studies show that the main goal of postoperative nutritional support is to achieve anabolism in the short term because insufficient intake of calories and protein can reduce the weight and muscle mass of the body and lead to an increased risk of infection and weakening of the immune system (Typpo et al. 2015; Boctor et al. 1999; Newcombe and Fry-Bowers 2017).

Determining energy needs is an essential principle in post-surgery nutritional support because TEE affects nutritional status, therapeutic interventions, and the severity and type of disease before, during, and after surgery (Nydegger et al. 2009) (Table 1).

For example, studies show that infants under extracellular membrane oxygenation (ECMO) have higher REE than controls (Shew et al. 1999). The rate of increase in studies is contradictory. One study showed that in infants supported by ECMO, REE increased to 89 kcal/kg/day (Keshen et al. 1997), whereas in another study, REE was increased to 55 kcal/kg/day in neonates supported by ECMO compared with the control group (Jaksic et al. 2001). In another study, infants who underwent cardiopulmonary bypass had an REE of approximately 30% higher than the control group (74 vs. 58 kcal/kg) (De Wit et al. 2010). Studies have also reported that the rate of protein catabolism increases by more than 100% (approximately 2.3 g/kg/day) compared to healthy infants (Shew et al. 1999; Keshen et al. 1997). In another study, from days 0 to 4 after the Norwood method, it was reported that infants who received the least calories had the most catabolic activity in the early hours after surgery. However, it was only on day three after surgery that a balance was struck between energy intake and consumption (Li et al. 2008). Petrillo Albarano et al. report that achieving nutritional support goals may take up to 9 days. During this time, an imbalance in macronutrient and micronutrient intake compared to energy consumption can reduce wound healing, cardiopulmonary function, and the immune system (Kogon et al.

2007). The most critical barriers to receiving nutritional support are fluid restriction and hemodynamic instability (Typpo et al. 2015).

Another barrier is the concern for intestinal ischemia after the onset of nutritional support; in the past, many providers were reluctant to feed infants with ECMO. However, this delay in providing nutritional support has been reduced from 67 h after the start of ECMO in 1997 to 40 h in 2001 (Hanekamp et al. 2005a). Because studies show that intestinal hormones respond well after the start of EN (Hanekamp et al. 2005b), nutritional support is well tolerated (Piena et al. 1998), and nutrition does not impair intestinal integrity (Piena et al. 1998; Kalra et al. 2018).

Malnutrition and poor weight gain are important factors in reducing the healing process of the disease, wound healing, and increasing the length of hospital stay (Fitria et al. 2019). Due to changes in patients' clinical status, it is recommended to evaluate indirect calorimeters several times a week and, if IC is not available, estimate equations (Nydegger et al. 2009; De Wit et al. 2010). However, it should be noted that these equations underestimate the energy and protein required by patients and, as a result, lead to weight loss, increase the duration of dependence on the respiratory system, and increase the length of hospital stay (Mehta and Compher 2009). Other factors associated with poor nutritional support outcomes include lower weight before surgery, surgery near the aortic arch, duration of postoperative intubation (Hofner et al. 2000; Sables-Baus et al. 2012), duration of surgery (Indramohan et al. 2017), the onset of oral feeding in the first few days after surgery (Sables-Baus et al. 2012), single-ventricle physiology (Kogon et al. 2007; Williams et al. 2011; Davis et al. 2008), risk adjustment for congenital heart surgery (RACHS) (Kogon et al. 2007), as long-term intubation (due to swallowing disorder) (Pierre et al. 2010), and cross-clamp time (Medoff-Cooper and Ravishankar 2013; Sables-Baus et al. 2012).

Although it is not clear exactly how the score RACHS and cross-clamp time have a negative impact on nutrition outcomes, patients are likely to experience early growth and oral malnutrition (Fitria et al. 2019; Mitting et al. 2015; Natarajan et al. 2010). Studies show that patients with HLHS have high nutritional side effects (Kogon et al. 2007; Davis et al. 2008). Norwood also has a risk of vocal cord injury and paralysis, leading to poor nutrition (Bejiqi et al. 2017). If the patient's needs cannot be met by oral feeding, nutritional support should be provided through EN or PN (Alakeel et al. 2021). Central venous access is typically required to provide adequate energy and protein without over-administration of fluids in PN (Tume et al. 2018).

The most crucial primary concern in PN is the increased risk of liver injury and infection (Ayers et al. 2014). Some postoperative complications, such as vocal cord injury and chylothorax, can prevent the achievement of nutritional support goals in CHD (Alten et al. 2015; Foz et al. 2021; Savla et al. 2017). Vocal cord injury can occur due to prolonged intubation or after aortic arch reconstruction or Norwood operation in patients with hypoplastic left heart syndrome (Slicker et al. 2013; Skinner et al. 2005). Possible causes of chylothorax can be thoracic duct damage, increased right pressure, and central venous thrombosis (Savla et al. 2017; Panthongviriyakul and Bines 2008).

The chylous fluid contains high triglycerides, lymphocytes, and proteins, including immunoglobulins and coagulation factors (Bhardwaj et al. 2018). Therefore, increased drainage leads to malnutrition, electrolyte disturbances, blood coagulation disorder, poor wound healing, and debilitated immune systems (Zuluaga 2012; Katanyuwong et al. 2009). The postoperative nutritional support algorithm is summarized in Fig. 1 (Tables 3, 4, 5 and 6).

Table 3 Recommended calorie and protein intake for patients with CHD (Vichayavilas et al. 2013)

Age	Intubated REE (kcal/kg)	Extubated activity (kcal/kg)	Protein critical illness (g/kg)
Preterm	50–60	90–120	3.5–4
0–12 month	55	90–120	2.5–3.5
1–3 years	55	75–100	2–2.5
4–6 years	45	65–90	2–2.5
7–10 years	40	55–70	1.5–2
11–14 years	30	40–55	1.5–2
15–18 years	30	40–55	1.5–2
15–18 years	25	30–40	1.5–2

Table 4 Recommended macronutrient amounts for patients with CHD in PN (Wong et al. 2015)

Macronutrients	Age/weight	Target dose (g/kg/day)
Protein/amino acids	Neonate	1.5–4
	0–1 month	1.5–3
	1 month–3 years	1.5–2
	13–18 years	1.5
Lipids (25–40% of non-protein calories)	0–2 years	3–4
	>2 years	2–3
Carbohydrates (60–75% of non-protein calories)	<3 kg	18
	3–10 kg	16–18
	10–15 kg	12–14
	15–20 kg	10–12
	20–30 kg	<12
	>30 kg	<10

Table 5 Recommended criteria for cautious use of PN (Anderson and Beekman 2015)

Hyperglycemia	Glucose>300 mg/dL
Azotemia	BUN >100 mg/dL
Hyper osmolality	Serum >350 mOsm/kg
Hypernatremia	Na >150 mEg/L
Hypokalemia	K <3 mEg/L
Hyper chloremic	Cl >115 mEg/L
Hypo chloremic	Cl <85 mEg/L
Hypophosphatemia	Phos <2 mg/dL
Acidosis/alkalosis	

Table 6 Inpatient parenteral nutrition monitoring (critical/acute care) (Martindale et al. 2009)

	Suggested frequency	
Variables	Initial period	Later period
Weight	Daily	Weekly
Serum electrolytes	Daily	Daily 1–2/week
Blood urea nitrogen	3-week	Weekly
Serum total calcium or ionized, Ca^{+}, inorganic phosphorus, magnesium	3-week	Weekly
Serum glucose	Daily	3-week
Serum triglycerides	Weekly	Weekly
Liver function enzymes	3-week	Weekly
Hemoglobin, hematocrit	Weekly	Weekly
Platelets	Weekly	Weekly
WBC count	As indicated	As indicated
Clinical status	Daily	Daily
Catheter site	Daily	Daily
Temperature	Daily	Daily
I&O	Daily	Daily

Management of Chylothorax

Chylothorax is one of the most important complications after surgery, and its rate has been reported from 1% to 9% (Zuluaga 2012). Chylothorax leads to severe and long-term deficiency of protein, fat, fat-soluble vitamins, inadequate nutritional support, increased length of hospital stay, and increased costs incurred by the patient and the health care system (Czobor et al. 2017). Chylous is a milky liquid with a triglyceride level in pleural fluid more significant than 1.1 mmol/L and a ratio of pleural fluid triglyceride level to serum triglyceride level greater than 1 mmol/L (Hermon et al. 2019). Also, the number of white blood cells is more than 1000 cells per milliliter, and the lymphocyte count is more than 80% (Bhardwaj et al. 2018). It is not clear how many of the above criteria and how much drainage are needed to begin the intervention. In general, an intervention model can be proposed

based on the amount of output volume and the change in chylous composition (Reisenauer et al. 2018). The high-volume output (discharge of more than 10 mL/kg per day) and the low-volume output, and the next step is to change the diet to a diet with medium or low-fat triglycerides to the change is in the composition of chylous.

Management of chylothorax after cardiac surgery may include a range of conservative diet modification management, with or without concomitant non-surgical medical administration, including medium-chain triglyceride-enriched or total parenteral nutrition.

Dietary management often begins with a decrease in long-chain fatty acid (LCT) intake and increased medium-chain triglyceride (MCT) intake. Because MCTs are absorbed and transported through the portal vein instead of the lactate, they bypass the lymphatic system. This dietary modification reduces the flow of chylomicrons through the thoracic pathway.

If there is no reduction in chylous drainage, it is started for nothing by mouth (NPO) and TPN patients, and if there is no response, octreotide is added to the NPO and TPN strategy. The use of octreotide is mainly for patients with congenital chylothorax. Although the exact mechanism of octreotide use in congenital heart surgery is still unknown, many studies support its use. Some studies use methods such as pleurodesis or thoracic duct closure, which are not feasible in patients with CHD due to the anatomical diversity of the lymphatic system. Recently, the using catheter has been reported to identify potential shale leakage damage in the affected lymph duct and the ability to target directly in the affected area. Although the results are promising, more studies are needed. There is disagreement about the replacement of shale constituents (e.g., albumin, immunoglobulins, fibrinogen, and other proteins and coagulation factors) or the volume of fluids and electrolytes lost. Although the replacement of electrolytes is common in both intensive care and inpatient settings, the results for other compounds are controversial.

In a study of patients with chylothorax who accidentally received immunoglobulin supplementation, no difference was found in the results. However, more studies are needed to supplement the missing compounds. In infants who are breast-fed or formula-fed, treatment includes (Van Der Bom et al. 2011) a mixture of breast milk with MCT-fortified formula (Fogg et al. 2016; Lessen 2009; Bouma and Mulder 2017), a formula containing MCT/LCT ↑ (Biewer et al. 2010; Shin et al. 2020; Church et al. 2017), or (Tabib et al. 2019) both. In children and adolescents who do not receive formula, a low-fat diet is recommended (Church et al. 2017; Caserío et al. 2010; Ahmed 2021). Although added MCTs can provide extra calories, over-intake of MCTs can reduce the intake of essential fatty acids (EFA). Therefore, the recommended diet should have the minimum required amount of EFA (Densupsoontorn et al. 2014). Although there is still no consensus on the content, components, and duration of the low-fat diet, studies reported that performing a diet intervention for 10 days to 6 weeks has had promising results (Katanyuwong et al. 2009; Shin et al. 2020; Ahmed 2021; Gaudiza et al. 2006).

Conclusion

Patients with CHD are a highly susceptible group to malnutrition. Therefore, early initiation of oral, enteral, parenteral, and trophic nutritional support is an essential principle in patients with CHD before and after surgery. Adequate and adequate nutritional support by improving growth and reducing malnutrition, infection, length of hospital stays, and mortality. In this study, the principles of nutritional support are summarized algorithmically based on the latest clinical evidence. However, due to the wide variety of forms of CHD and its complications, more clinical studies are needed to reduce the concern for early initiation of nutritional support.

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Future Approaches for Anesthesia in Congenital Cardiac Surgery and Interventional Procedures

Andrew Giustini, Ali Dabbagh, and Alexander Robert Schmidt

Abstract

With emerging advances in congenital heart surgery and interventional pediatric cardiology, the demand for cardiac anesthesia in pediatric and adult patients has increased over the past decade. New complex surgical techniques and minimally invasive interventional approaches in children with an increasing morbidity have led to greater challenges for anesthesiologists. The aim of this chapter is to highlight new and safer approaches, describe evolving devices, and suggest modern techniques for the anesthetic management of pediatric and adult patients with congenital heart disease (CHD). This chapter should encourage the support of new innovations and inspire further research in the field.

Keywords

Future approaches · Personalized medicine · Artificial intelligence · Machine learning

Future Approaches in Airway Management

Appropriate and safe management of the pediatric airway is one of the most important tasks in pediatric anesthesia. A rapid response to airway management problems during induction (e.g., bag mask ventilation or intubation) is necessary to maintain adequate oxygenation due to the known low functional residual capacity in newborns and infants (Sands et al. 2009; Hardman and Wills 2006). Especially in patients with congenital heart disease (CHD), the risk of an adverse outcome is increased due to limited oxygen reserve resulting from decreased cardiopulmonary function or lower saturations due to mixing lesions; this may put additional stress on the anesthesiologist during induction and intubation.

Based on a retrospective review, the incidence of a difficult laryngoscopy in the pediatric population was reported to be 1.35%, but significantly higher in CHD patients at 3.6% (Heinrich et al. 2012). Since 30% of CHD is related to genetic syndromes, patients with CHD often also present with craniofacial anomalies (Eskedal et al. 2007).

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Down syndrome, Noonan syndrome, Di-George, CHARGE, or VACTERL are some of the most common genetic syndromes associated with CHD and patients with these genetic syndromes have various degrees of airway malformations.

It is of great relevance that difficulties with pediatric airway management present a major cause for anesthesia-related cardiac arrest or brain injury in the perioperative cardiac arrest registry (Bhananker et al. 2007) and the American society of anesthesiologists (ASA) closed claims analysis (Jimenez et al. 2007; Mamie et al. 2004). Fiadjoe et al reported that more than two intubation attempts were associated with a higher failure and increased complication rate and thus concluded that the first attempt is the best attempt (Fiadjoe et al. 2016). For this reason, it is of great importance to have the best preparation for intubation success and reducing the risks of adverse airway events.

In the past years, video laryngoscopy (VL) has become readily available and is recommended for the management of difficult airway scenarios. However, it is rarely recommended for routine use in daily practice. Based on the findings of a recently published study comparing standard direct laryngoscopy (DL) with VL, the use of VL in pediatric patients should be considered for the management of both the normal and difficult airways. This multicenter, randomized controlled trial showed a better first-pass intubation success and was associated with fewer complications (Garcia-Marcinkiewicz et al. 2020); this was especially the case in children less than 6.5 kg. Based on these findings and the fact that pediatric patients with congenital heart disease are a high-risk population, the best and safest airway management approach should be chosen. Another advantage resulting from the routine use of VL for "normal" airways is that staff members are trained in its use and are then confident with and prepared for difficult airway situations and the use of VL. Using a device like the C-Mac (Karl Storz, Tuttlingen, Germany) enables simultaneous DL and VL and has the advantage that the airway can be graded via DL, while conversion to VL is possible in the same attempt. This device also has benefits in educational setting and academic centers, allowing the supervising physician to monitor the airway view the trainee is obtaining during laryngoscopy.

Future Approaches for Arterial Catheter Placement

During virtually all cardiac surgical procedures the placement of an arterial catheter is essential, and it allows for continuous monitoring of the systemic arterial pressure as well as sampling of arterial blood gases. In neonates and infants, the placement of an arterial catheter can be technically challenging due to the small diameter of the vessel and the difficulty of localizing it via palpation. The difficulty is increased after multiple attempts leading to a hematoma (Rhee and Berg 1995), in patients who require multiple procedures and/or patients who present with small, obstructed, or stenotic arteries (Aldridge and Gupta 1992). Since the introduction of, and readily available, ultrasound devices, the failure rate of arterial catheter placement has decreased significantly (Schwemmer et al. 2006; Aouad-Maroun et al. 2016). However, in some cases, arterial catheter placement is not successful with the first attempt and, hence, remains challenging. One reason might be a non-ergonomic setting in the operating room (OR) or procedural room, as well as inexperienced hand–eye coordination. This issue was addressed by Jang et al in a prospective, single-blinded, randomized controlled, single-center study comparing conventional ultrasound screen use with the use of a head mounted display (smart glasses) for radial artery catheterization (Jang et al. 2021). In the study, smart glasses displayed the ultrasound image in the field of view while the person placing the catheter was looking at the insertion site. The study showed a higher first-attempt success rate with the smart glasses (87.9% vs. 72.4%; $p = 0.036$), a shorter first-attempt procedure time with the smart glasses (median, 33 s vs. 43 s; $p = 0.007$), and an overall lower complication rate with the use of the smart glasses (5.2% vs. 29.3%; $P = 0.001$). This study shows how modern technology can increase our success rate for technically challenging procedures and should be

considered for standard use in highly demanding setting and educational environments.

Non-Invasive Measurement of Kidney Perfusion

During cardiac surgery, the risk of acute kidney injury (AKI) due to renal hypoxia (Evans et al. 2013) is increased and it is known that AKI is associated with a significant rise in morbidity and mortality (Machado et al. 2014; Gaffney and Sladen 2015; Englberger et al. 2011). Hence, early or even real-time detection of renal hypoxia and threatening AKI is desirable and important to timely initiate therapy, and thus reduce morbidity and mortality. With currently available tests, identification of AKI is often delayed and performed postoperatively. Silverton et al presented an interesting and promising approach to detect renal hypoxia in a recently published study (Silverton et al. 2021).

Based on the anatomy and physiology of the kidney, the oxygen partial pressure of the urine first excreted in the urinary collecting ducts is similar to that of the renal medulla (Evans et al. 2014)—the region most vulnerable to hypoxic injury. Earlier publications demonstrated a good correlation of reduced renal blood flow or decreased cardiac output (CO) with the urinary oxygen partial pressure (Kainuma et al. 1990; Lankadeva et al. 2016), as well as the predictive value of urinary oxygen partial pressure for postoperative AKI in patients after cardiac surgery (Zhu et al. 2018). However, these studies used an invasive measuring technique not feasible for the operating room. Therefore, Silverton et al developed a new, non-invasive prototype monitor capable of measuring oxygen partial pressure in the urine. The probe is placed between the urinary catheter and collection bag and allows for real-time measurement of urinary flow rate, oxygen partial pressure, as well as temperature. In a pilot study, they collected the data during surgery and for the first 24 hours after surgery. Based on their findings they concluded that the presented approach is feasible in 95% of the cases and that a low urinary oxygen partial pressure after cardio-pulmonary bypass (CPB) could be associated with the development of AKI.

Silverton et al and their technique demonstrate great potential of novel techniques for monitoring renal perfusion during cardiac surgery. Together with initiation of adequate clinical management, the role of such a real-time monitor may have a significant impact on patient morbidity and mortality. At the current state, further studies are required to fully evaluate the potential of this promising method. In the future, it may be included in the routine monitoring for CHD patients undergoing cardiac surgery on cardiopulmonary bypass.

Non-Invasive Measurement of Hemoglobin

Patients with CHD often require higher levels of hemoglobin due to their pathophysiology. Therefore, it is important to closely monitor hemoglobin levels during all procedures (cardiac, non-cardiac, interventional cardiology and imaging), especially in neonates and infants where minimal blood loss (i.e., repetitive blood gas sampling) or administration of intravenous fluids can cause major alterations of the hemoglobin level. Unfortunately, clinicians are often limited to invasive tests that only provide intermittent and delayed hemoglobin results. With the availability of transcutaneous sensors allowing for simultaneous measurement of peripheral oxygen saturation (SpO_2) and non-invasive capillary hemoglobin SpHb, real-time monitoring of hemoglobin can improve patient safety, decrease the need for blood draws, save time, and modify transfusion practices. Studies have shown the reliability of these sensors in acute and chronic conditions: During pediatric trauma with solid organ injury, the SpHb shows a high correlation with the hemoglobin measured in the lab with respect to the hemoglobin trend during stable as well as transfusion conditions (Welker et al. 2018) and in the pediatric intensive care unit (ICU) it is of use for continuous monitoring of

patients at risk of bleeding by showing a good correlation between SpHb and laboratory-measured hemoglobin (García-Soler et al. 2017).

Based on these findings, it is suggestive that SpHb could be of use in patients with CHD and should therefore be considered for the following cases:

- All neonatal cases—to reduce the amount of blood samples drawn for hemoglobin monitoring.
- All cases with expected high blood loss—to allow for rapid response to changes in hemoglobin levels.
- All cases that are performed *without* an arterial catheter or central venous catheter and when hemoglobin cannot be easily monitored otherwise.
- All cases for CHD patients who require higher levels of hemoglobin.

With this recommended practice, patient safety during anesthesia can be improved and medical costs can be reduced (Martin et al. 2016; Ribed-Sánchez et al. 2018). And even if only used as a trending device, this future approach can be of value to trigger invasive measurement of hemoglobin for decision-making on the need for blood transfusion.

Cardiometry and Other Non-Invasive Methods for Cardiac Output Monitoring

Monitoring of cardiac output and related parameters such as stroke volume (SV) and vascular resistance is important in making hemodynamic management decisions during congenital heart procedures. Traditionally, techniques such as thermodilution measurements, continuous cardiac output pulmonary artery catheters, and transesophageal echocardiography have been used to measure these parameters during surgery. However, in infants and children, it can be impractical or impossible to routinely obtain those measurements using invasive catheters during cardiac surgery due to patient size and cardiac anatomy. Recently, less invasive and non-invasive measurement techniques for these physiologic parameters have been developed.

Cardiometry is a method of estimating parameters such as cardiac output, which relies on thoracic bioimpedance measurements. Essentially, these monitors use surface electrodes to measure impedance changes in a patient's thorax throughout the cardiac cycle, and then use proprietary algorithms (different for each device manufacturer) to estimate physiologic parameters such as cardiac output, stroke volume index, and oxygen delivery (Ghanem and El-Hefnawy 2021). Numerous studies have shown that cardiometry demonstrates good accuracy in monitoring and trending these parameters in various populations, including cardiac output in preterm infants (McGovern and Miletin 2018), cardiac index in all ages of children in the operating room (Coté et al. 2015), and in assessing fluid responsiveness of septic pediatric ICU patients (Lalitha et al. 2021). This non-invasive monitor shows promise as another tool for monitoring the physiology of intraoperative congenital heart disease patients.

Another novel technology for advanced monitoring of cardiac output (CO), stroke volume (SV), and stroke volume variation (SVV) that has been validated in children is pulse wave analysis (Kim et al. 2006). Kouz et al extensively summarize and review this technology (Kouz et al. 2021). Briefly, pulse wave analysis comprises a group of technologies that use the pulse wave from either an arterial catheter, a non-invasive finger cuff, or surface radial artery cuff to continuously monitor cardiac output (Kouz et al. 2021). These technologies are classified by Kouz et al as either "invasive," "minimally invasive," or "non-invasive based," based on the monitoring device, and then subcategorized as "externally calibrated," "internally calibrated," or "uncalibrated" based on the method of calibration (Kouz et al. 2021). The most invasive—and most accurate—requires both an arterial catheter and central venous catheter to perform either thermodilution or lithium dilution measurements to calibrate the cardiac output measurements and yield similar accuracy to pulmonary artery catheter thermodilution (Reuter et al. 2010; Jonas and

Tanser 2002) and are classified as "invasive externally calibrated" devices by Kouz et al (Kouz et al. 2021).

"Minimally invasive" devices require only an arterial catheter and are either internally calibrated based on patient characteristics such as demographics, height, and weight or are "uncalibrated" and only analyze the arterial waveform to derive CO measurements without information about the patient (Kouz et al. 2021; Jozwiak et al. 2018). Both calibrated and uncalibrated minimally invasive measurements are susceptible to error from measurement errors such as damping of the arterial waveform, and calibrated measurements are less accurate if patient characteristics are outside of the norms on which the technology was designed (Kouz et al. 2021; Jozwiak et al. 2018; Saugel et al. 2020; Slagt et al. 2014).

"Non-invasive" devices use a cuff on the finger or a sensor on the skin overlying the radial artery to measure the pulse waveform and are internally calibrated based on patient characteristics and demographics (Kouz et al. 2021; Jozwiak et al. 2018). The finger cuff modulates its pressure during the cardiac cycle to keep the blood volume in the finger constant, which allows the cuff to measure the characteristics of finger arterial flow throughout the cardiac cycle and estimate the arterial pressure waveform. The radial sensor performs a similar function to the finger cuff over the radial artery instead of the finger. Limitations on accuracy are like those in "internally calibrated, minimally invasive" devices, with additional limitations based on patient pathophysiology, especially that which limits distal perfusion, such as peripheral vascular disease or use of vasoactives (Kouz et al. 2021; Saugel et al. 2014; Monnet et al. 2012).

Artificial Intelligence and Machine Learning in Pediatric Cardiac Anesthesiology

Machine learning refers to a group of technologies that use models that aid computers in making predictive models and analyzing datasets (Connor 2019)—these technologies are a subset of artificial intelligence and should be regarded as ever-evolving decision support tools (Görges and Ansermino 2020). These technologies involve the use of training datasets that are used to create a model. Subsequently, the model is tested with a validation dataset to assess its accuracy. Machine learning has classically depended on supervised techniques, where investigators choose the features of the datasets they believe to be relevant and build models based on those features. Newer machine learning techniques such as deep learning and neural networks often involve unsupervised techniques where the training dataset is analyzed autonomously to create a model and the investigator may not know which factors are considered when the algorithm makes predictions (Hashimoto et al. 2020). When interpreting studies using machine learning and artificial intelligence techniques, important limitations to note are that models are limited by the quality of their training datasets and of the algorithms used to build those models. Artificial intelligence and machine learning tools are unlikely to replace anesthesiologists in the foreseeable future, but they will likely be incorporated as *Clinical Decision Support* (CDS) tools we can use to provide better care (Alexander and Joshi 2018).

Machine learning is currently being used in applications in sectors such as finance, social media, and chemistry, as well as multiple aspects of health care. In anesthesiology, the applications range from predicting postoperative morbidity and mortality (Mathis et al. 2018) to minimizing intraoperative hypotension (Wijnberge et al. 2020; Joosten et al. 2021), monitoring the pediatric airway and predicting airway complications (Matava et al. 2020), and identification of structures during regional anesthesia (Bowness et al. 2021) and neuraxial anesthesia (Oh et al. 2019). Hashimoto and colleagues present a scoping review discussing the uses of artificial intelligence in "depth of anesthesia monitoring, control of anesthesia, event and risk prediction, ultrasound guidance, pain management, and operating room logistics pp. 380" (Hashimoto et al. 2020).

There are multiple technologies enabled by machine learning and artificial intelligence that may soon be applied to improve anesthetic care

for patients with congenital heart disease. Smart glasses and augmented reality can be used for both realistic simulation and improved success for vascular access (Jang et al. 2021; Rochlen et al. 2017). Difficult airway prediction and management may become more standardized (Matava et al. 2020). Predictive models will be used to help risk stratify patients (Görges and Ansermino 2020; Mathis et al. 2018) and help guide timing of interventions. These techniques will also allow for more objective analysis of echocardiographic data (Liu et al. 2020). Through analysis of intraoperative data, machine learning algorithms may be used to warn of impending hemodynamic or respiratory compromise (Hashimoto et al. 2020; Wijnberge et al. 2020; Sippl et al. 2017) and even to help manage hemodynamics (Joosten et al. 2021).

Personalized Diagnostics in Congenital Cardiac Patients

In congenital cardiac surgeries, several abnormal anatomic structures are leading to pathophysiologic perturbations and "pathomechanisms," presenting as a clinical disease. The use of personalized diagnostics is creating a paradigm shift in congenital heart disease diagnostics through various approaches (Sezari and Dabbagh 2019). First and foremost, the introduction of 3D imaging has created an interesting option to evaluate the underlying abnormalities in all aspects of the preoperative period; this improves not only the surgical aspects of care, but also the anesthesiologist's work. For example, 3D imaging can aid in management of the potentially difficult airway in a patient with congenital anatomic lesions in the head and neck, or for exact targeting for placement of arterial and venous lines. Second, using molecular, genomic, epigenomic, and "multi-omics" markers, preoperative evaluation of the patient would be much more precise with personalized tailoring of the anesthesia plan; the perioperative and anesthetic care would be managed using a personalized clinical plan. Hence, the word "anesthesiomics" could fit such an approach (Dabbagh 2020). This personalized approach could lead to the novel approaches for perioperative care based on each patient's unique characteristics.

Third, a combination of "cardiogenomics, cardioproteomics, cardiometabolomics," and other cardiovascular-related—omics, with artificial intelligence and machine learning, regenerative medicine, and cell therapy will revolutionize the future of congenital heart diseases when combined with other clinical diagnostics (Jain 2017; Madeddu et al. 2019). Last, personalized diagnostics lead to sensitive screening and diagnostic tests with significant changes in clinical care (Manickaraj and Mital 2012; Agrò et al. 2021). These are further discussed in the next section.

Personalized Pharmaceutics and Individualized Anesthesia Management: Its Role in the Future

Anesthetizing neonates, infants, and children for cardiac and non-cardiac surgeries is challenging and requires thorough assessment and planning. These patients are in a vulnerable stage of organ growth and development, and they are at significant risk of perioperative complications. To achieve the goal of sedation and analgesia, administration of anesthetic agents and drugs is derived from evidence and experience. Based on our individual experience, we can all report on our patients' differences for anesthetic requirements for induction and maintenance, as well as the time they need to recover from an anesthesia. An explanation may be found in predictable patient-related factors (age, body mass index, organ function [heart, liver, kidneys], or medication history), drug-related factors (pharmacokinetic and pharmacodynamic properties), or the surgical/procedural related factors (i.e., type, complexity). However, there are also other unpredictable factors impacting patient outcome. Most of the drugs we use can cause adverse events, often unpredictably und not necessarily in dose-dependent manner. These adverse drug effects are of great importance since they represent a major cause of iatrogenic morbidity and mortality in anesthesia. About 20% of reported adverse

drug reactions are believed to occur because of existing genetic factors. The presence of different gene polymorphisms encoding for the drugs' action site, signaling pathways, or metabolic enzymes can have a significant impact on anesthesia outcome. The understanding of genetic variations, and their clinical consequence would allow to apply a personalized approach, possibly improving patient outcomes and reducing adverse drug reactions.

Research in the field of pharmacogenomic testing aims to identify the patient's genetic sequence and how this sequence interacts with anesthetics. Currently, genes, proteins, and allelic variants have been described for volatile anesthetics, intravenous anesthetics, local anesthetics, sedatives, opioids, and muscle relaxants. Table 1 summarizes genetic polymorphism for the most common intravenous anesthetics and the effects.

The intention of a personalized approach is to identify the correct drug at the appropriate time for the right patient. This vision requires genetic testing once in a patient's lifetime bearing results that can be used forever. Based on the genetic findings, specific pharmacologic properties can be investigated, and then appropriate decisions can be made with regard to drug dosing. Until further research brings clarity into this field, personalized medicine remains an approach of the distant future. However, other interesting strategies have been published presenting an individualized approach to improving patient outcome.

One approach for individualized management was recently published (Joosten et al. 2021) and demonstrated that a computer-assisted individualized hemodynamic management during intermediate- to high-risk non-cardiac surgery significantly reduced the incidence of intraoperative hypotension compared to a manually controlled goal-directed approach. The algorithm uses a closed-loop system with invasive arterial pressure monitoring and titrates a norepinephrine infusion based on the arterial pressure margins set. In addition, a separate decision support system (based on stroke volume variation and other parameters) recommends mini-fluid challenges to prevent from hypovolemia masked by the norepinephrine infusion. This example shows one possible approach for a personalized anesthesia management strategy.

Table 1 Genetic polymorphism with clinical relevance for selected anesthetic drugs (Source: Elens et al. 2013; Zhong et al. 2017; Dinis-Oliveira 2017; Mieda et al. 2016)

Drug	Gene with polymorphism	Effect
Midazolam	CYP3A4, CYP3A5	Reduced clearance
Propofol	5HT2A	Shorter onset time
Ketamine	CYP2B6	Reduced metabolism
Fentanyl	CYP3A4	Difference in drug response

Summary

As procedures to care for patients with congenital heart disease evolve and children with more severe illness and comorbidities are cared for, anesthetic techniques must also advance. Progress in the safe care of these patients is continuous yet evolving, and the congenital cardiac anesthesiologist must integrate new techniques as they become available. Just as the use of technologies such as ultrasound, near-infrared spectroscopy, and novel hemostatic agents has improved the safety of pediatric cardiac anesthesia over the previous decades, novel technologies will further change practice going forward.

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Pediatric Cardiac Surgery in Emerging Countries

William M. Novick and Marcelo Cardarelli

Abstract

The infant mortality rate (IMR) of a country is a commonly used indicator to reflect the health status of a population. While nearly 70 countries have managed to achieve single-digit IMRs, close to 124 emerging countries continue to have IMRs in the 2 and even 3 digits. So, a significant proportion of children born with congenital heart disease in Asia, Africa, and Latin America do not receive proper diagnosis or treatment.

Only 30 countries are providing appropriate care to all their patients while 1.5% of children born outside of industrialized countries receive needed surgery. Clearly, a substantial shortage of physicians, healthcare professionals, facilities, and budgets is dedicated to the management of this significant problem.

In this chapter, the plan to designing and "Developing a Sustainable Congenital Heart Center in an Emerging Country" and a "Success Story" are discussed.

While in the short term this problem is unlikely to be solved, surgical/educational humanitarian campaigns combined with adequate locally budgeted resources and a sustainable plan may, in the long term, create the conditions by which most children born with heart defects in the developing world could be diagnosed and treated in time to have a full and productive life.

Keywords

Infant mortality rate · Congenital heart disease · Sustainable congenital heart center · Emerging countries · Developing world

The Burden of Congenital Heart Disease in the World and Emerging Nations in Particular

The infant mortality rate (IMR) of a country, defined as the number of infants dying before reaching 1 year of age for every 1000 children born alive during the same year, is a commonly used indicator to reflect the health status of a population.

While nearly 70 countries have managed to achieve single-digit IMRs, close to 124 emerging

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countries continue to have IMRs in the 2 and even 3 digits.

Countries making an epidemiological transition by conquering the prevailing and preventable causes of infant mortality through simple measures, such as sanitation and vaccines, must still struggle to achieve single-digit IMRs. Many factors contribute to a persistently high neonatal and infant mortality rates, and root causes are compounded and assorted, but a significant contributor to the infant death toll is the uniform incidence of birth defects across geographical, socioeconomic, and political borders (Gilboa et al. 2010).

Globally, close to 2% of all neonatal death can be attributed to cardiac malformations (Rao 2007); therefore, new public health approaches and strategies must be developed to deal with the devastating effects of congenital heart disease (CHD).

Using publicly available data (The Worldbank 2013; CIA 2013; WHO 2013), we calculated the yearly incidence of severe/moderate congenital heart disease for 180 countries. Based on 2009–2010 population data, the incidence of CHD was estimated by multiplying the number of live births times the prevailing rate of CHD among newborns.

Since mild forms of CHD rarely require interventions in the first year of life, hence not affecting the infant mortality rate of a nation, they were excluded from our calculations.

Based on a published review of 62 publications on the incidence of CHD, we adopted for our calculations a very conservative incidence rate of 6 moderate/severe CHD cases per 1000 children born alive (Hoffman and Kaplan 2002). As a result, we have calculated an incidence of 809,936 children born with moderate or severe forms of CHD and requiring surgical treatment or catheterization every year.

With a global burden of 810,000 new cases every year, the question then becomes, how many of those new patients do receive the proper intervention/surgery, and it is here where the numbers are less clear.

We accessed the list of self-registered pediatric cardiac surgeons on the Cardio-Thoracic Surgery Network (CTSNet) as a proxy for the availability of pediatric cardiology/pediatric cardiac surgery services in any given country. The Cardio-Thoracic Surgery Network (CTSNet) is a not-for-profit organization jointly overseen by The Society of Thoracic Surgeons, the American Association for Thoracic Surgery, and The European Association for Cardio-Thoracic Surgery (EACTS) as well as numerous cardiothoracic surgery organizations from around the world (http://www.ctsnet.org). The number of cardiothoracic surgeons who list themselves as practicing in the pediatric subspecialty amounts to 3200 around the world—a number that no doubt would become significantly smaller if we were to subject every self-listed pediatric cardiac surgeon to some stricter account of formal training experience and exclusive dedication. The second issue regarding the true number of available surgeons is given by the uneven geographic distribution of those specialists able to perform surgical procedures or manage treatment in these newborns.

While the calculated ratio of new patients born with CHD per congenital heart surgeon is 200/1 at the global level, the inequities are profound and dramatically different among continents. We found the most homogeneous distribution of surgeons in Europe where that ratio is close to 55 newborns with CHD/year per listed surgeon. Meanwhile, the American continent as a whole has a ratio of 91 newborns with CHD per listed surgeon, but with significant disproportions in the ratios between the North American continent and the rest. While the United States and Canada have a low ratio (41 children born with CHD per listed surgeon), Latin America and the Caribbean have significantly higher ones (193 newborns with CHD per listed surgeon). Yet, the most dramatic shortage of pediatric heart surgeons can be seen in Asia and Africa with ratios of CHD newborns to the surgeon of 486 and 1069, respectively. Oceania, on the other hand, has ratios comparable to those of developed nations (45 CHD newborns/year per listed surgeon).

Using a conservative estimate of 60 newborn children with CHD/surgeon ratio as a measure

that may convey the ability of health services to deal with a modern approach to the burden of this disease, we could speculate that only 30 countries are providing appropriate care to all their patients. This represents appropriate diagnosis/treatment for 68,827 patients born every year with moderate to severe CHD out of 809,000. It is estimated that as low as 1.5% of children born outside of industrialized countries receive needed surgery (Leon-Wyss et al. 2009). Clearly, a substantial shortage of physicians, healthcare professionals, facilities, and budgets is dedicated to the management of this significant problem.

Shortages and Solutions

Human Resources

One of the most significant shortages to solve the problem of children and adults with CHD in emerging countries is the human factor. Unlike infrastructure (hospitals, operating rooms, intensive care units [ICUs], monitors, etc.) or supplies (oxygenators, sutures, sterile supplies), human resources require a significant time investment, besides the cost, never shorter than 5–10 years. Upon the decision of a Government, a Ministry of Health, or a local foundation to act upon the lack of congenital heart surgery services, given allocated resources, a building project may require anywhere between 1 and 3 years. Disposables, medications, sterile supplies, and instruments can be obtained, given enough economic resources, almost immediately. Human shortages (nurses, anesthesiologists, intensive care physicians, surgeons), on the other hand, are a very expensive item; it is in short supply and it requires anywhere from 4–10 years of tertiary education to build.

No amount of economic resources can speed up the process of knowledge accumulation and expertise gathering that these professionals need to transit before becoming proficient in the management of CHD, and it is only with long-term planning that any society can satisfy its healthcare need in this and many other complex areas.

Because of this reason, the diagnosis and treatment of CHD in children and adults in emerging countries currently depend heavily on the support of international charity organizations and the use of alternative training pathways to achieve self-sufficient centers.

Developing a Sustainable Congenital Heart Center in an Emerging Country

Models of Assistance

The options available to either improve pediatric cardiac services at an existing site or to engage in the development of a new program are numerous and should be tailored to the desires and capabilities of the local stakeholders (Dearani et al. 2010). Regardless of which model is decided upon, all participants must be fully vested in a long-term commitment.

Over the years we have employed four distinctive models of assistance, all having great benefits as well as drawbacks.

Education Abroad

Sending personnel abroad for education and training to centers of excellence for brief or extended periods has been used for years as a mechanism to initiate or improve a local program in pediatric cardiac care. The benefits of such a model are obvious. The trainees are exposed to centers practicing pediatric cardiac care in well-equipped institutions that have had many years to establish their programs. Typically, teams at these sites have matured into cohesive units that function seamlessly. Sending young inexperienced personnel into such situations can and does lead to excitement about returning home to provide similar services. However, without adequate leadership support at home, administrative commitment, and appropriate financing, this excitement rapidly disappears upon returning home to the realities of working in a low- and middle-income country (LMIC) health system. Language and cultural differences may interfere with optimizing the benefits that such an opportunity can

present. In several western countries, visits to centers of excellence may be observational only secondary to medico-legal issues and licensing. In the United States, direct patient care is unlikely unless the visitor has passed appropriate standardized tests and is in a position to be licensed locally. Such a program requires considerable time and financial expense (Novick et al. 2008). It is important that the person being chosen to receive this opportunity be sufficiently mature and knowledgeable to reap the benefits. We usually recommend that at least two individuals make these visits abroad to provide support to each other during the visit and to serve as the core for change upon return home. We have used this model to provide education to groups of physicians, nurses, and technicians from several countries (Croatia, Bosnia, Kazakhstan, Nepal, Ukraine).

Experienced Physician Returns to Lead Program

Individual senior physicians who have a desire to return home or simply a desire to assist a country in need after they have created a successful program abroad can have a major impact on program development in LMICs. The obstacles to adequate financing and political and governmental support remain, but having an experienced senior-level leader to advocate for and direct program development is extremely beneficial to overall program sustainability and success. We have employed this model in Honduras and Nicaragua.

Visiting Team of Specialists

The model most frequently used today is when a team of pediatric cardiac specialists visits a particular institution for a varying number of trips per year for an extended period. The composition of the visiting team is critical for success at every level. A visiting team must be cognizant that the receiving team will view them both positively and skeptically and realize that all aspects of the visit will be reviewed. Cultural, religious, and political differences may be present and the visiting team must respect these differences if the success of the program is to be complete. Our teams are typically comprised of senior-level pediatric cardiac specialists including surgeons, anesthesiologists, cardiologists, intensivists, ICU nurses and nurse practitioners, respiratory therapists, and, when needed, a biomedical engineer. Visits including travel time are usually limited to 2 weeks and local holiday and weekend work schedules are adhered to. Depending upon local infrastructure and personnel, one to three children receive operations daily and a similar number of catheterizations depending upon need.

The key difference between these trips and those commonly referred to as "surgical safari" is the frequency of trips annually (3–6) and the number of years committed to developing pediatric cardiac services (5–7). We have used this model in 34 countries and helped to develop independently functioning pediatric cardiac units in 53 different institutions. Not all programs have been successful and we have canceled 12 programs after the first 1–3 trips secondary to a variety of factors we deemed unacceptable.

One-Year Program

We developed a unique program assistance scheme whereby we embed a team of specialists in-country on a near-continuous basis for 12 consecutive months. The team consists of a surgeon, anesthesiologist, perfusionist, intensivist, and 2–4 ICU nurses/practitioners. The surgical component spends 1 month on-site, departs for 1–2 weeks, and returns for a month on a continuous type schedule for 12 consecutive months. The ICU team arrives with the surgical team and a portion of this team remains during the absence of the surgical team. Such a schedule allows for 41–42 weeks of surgical coverage and education and the ICU team spends 48 weeks on-site with breaks for holidays only. The purpose of this program is to provide immediate coverage for neonates and complex cases on a nearly continuous basis to countries with a population and birthrate that can provide sufficient clinical work. The result is a rapid expansion of services and a con-

centrated period of education and training. We have used this program in two countries to date, Iraq and Libya. Such a program is covered by both volunteers and dedicated full-time staff from the charity.

The decision of which model to use is dependent upon the local stakeholders' needs for clinical and educational services in addition to the financial support provided by the visiting and local teams. The philosophical and financial support by the hospital administration and Ministry of Health of the respective regions/countries is critical to program growth and eventual sustainability.

A Success Story

The cardiac unit at the Zaitsev Institute for General and Urgent Surgery serves both adults and children, draws from a population close to 2.9 million, and has the financial support of the Ukrainian National Academy of Medical Sciences. It has a single-plane cardiac catheterization laboratory, one dedicated operating room, and an eight-bed cardiac surgical intensive care unit (CSICU) with no separation of care between adults and children.

Our pediatric assistance program launched in May 2008 and it consisted of visiting international teams approximately every 3 months for 2-week period; it has been focused on five main areas:

1. On-site surgical and interventional activity with side-by-side training of the local team
2. Education (on-site lectures, Quality Assessment conferences, Morbidity and Mortality conferences)
3. Biomedical engineering support (donation of equipment and supplies, continuous engineering support)
4. Development of a teamwork culture with nurse empowerment and a horizontal hierarchy
5. Data collection

Using the Risk Adjustment for Congenital Heart Surgery-1 (RACHS-1) model of risk stratification (Jenkins et al. 2002) and reviewing patient data and demographics for the 7 years before our involvement (Period A: the year 2000–2008) and the 7 years since our assistance program was implemented (Period B: 2008–2015), we show an increase in the annual volume of cases and a trend toward treatment at a younger age (Table 1). Also, in Fig. 1 we can vividly visualize the increment in case of complexity with a significant decrease in mortality (66.7–11.7%) for category RACHS-3 cases ($p = 0.05$).

Table 1 The data on the eight common outcomes quality measures in 2709 of the surgeries carried out in 10 LMICs between January 2008 and June 2013

	Period A	Period B	*p*
Total number of RACHS-1 classifiable cases	154	767	
RACHS-1 classifiable patients/year (95% confidence interval)	19.3 (14.3–4.2)	95.9 (63.2–128.6)	<0.0001
Median age (in years)	7	1.3	

Note: Please refer to the text for further information

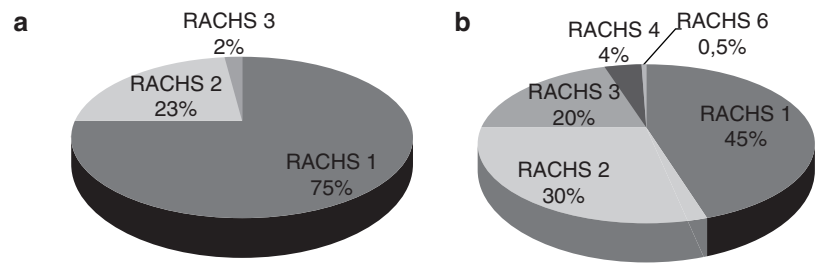

Fig. 1 (**a**) Period A (before program assistance). (**b**) Period B (after program assistance)

Analysis of the Five Main Areas of Program Assistance

On-Site Surgical and Interventional Activity

The principal purpose of an assistance program is not to perform, but to teach by working side-by-side with the local teams while performing. There is no theoretical or classroom-style teaching stronger than hands-on exercise. The establishment of a patient discussion conference is the first step in accomplishing this goal. All patients selected for intervention/surgery during the 2-week visit periods are open for discussion and relevant information is equally shared. We believe it is during this process of sharing the information available and the experiences of the most senior leaders of our teams that the hosting team benefits the most. While in occidental societies we believe that the opportunity to openly discuss and question the decision-making process is fundamental for the good outcome of the patients, it is not an exercise commonly carried out in other cultures. The agreement to question leadership and decisions is a learned habit that promotes good leadership skills while fostering change, keystones to the development of modern cardiac surgery centers.

Equally important is the shared experience in the operating room or catheterization suite. Our programmatic approach to the sharing/educating experience permits the transition of leadership roles over a variable period, from the visiting to the local team. We expect that while at the beginning of the program assistance implementation the visiting team (us) will lead and partake in most if not all of the interventions/surgeries, over time the local surgeon(s) and interventional cardiologist will share a larger proportion of responsibility in the decision-making and the actual doing of the procedure. Using the Kharkiv experience, the proportion of locally led surgeries during international assistance trips significantly increased from 0% in 2008 to 76.2% in 2010, finalizing with 100% locally led surgeries in 2015. Likewise, surgical milestones made by the local team with international team assistance include the first time as primary surgeon for a Tetralogy of Fallot full repair (2009), Complete Atrioventricular (AV) Canal repair (2011), and the Arterial Switch Operation (2012). Since 2010, a second local pediatric heart surgeon has also begun training as a lead surgeon.

It is important to consider that the volume and complexity of cases are kept up during the periods when we are not visiting and assisting, demonstrating a solid movement toward self-sustainability.

Education

The role of formal education should not be underestimated. Fundamental concepts must be mastered in the safe environment a classroom provides before being put to practice. We believe the introduction of nurses and perfusionists to the most updated concepts to be of essential importance. Constant improvement, a concept ligated to High-Reliability Organizations (HROs: organizations, such as airlines and nuclear power plants, that cannot afford the occurrence of even a single unwanted event), depends greatly on education and insight. Using this concept to develop a cardiac surgery center implies a trend toward zero tolerance for mishaps. Unwanted events are to be avoided by planning rather than coping with them by relying on multiple safety mechanisms.

At the core of high-reliability organizations (HROs) are five key concepts, which we believe are essential for any improvement initiative to succeed (Hines et al. 2008):

Sensitivity to operations*: Preserving constant awareness by leaders and staff of the state of the systems and processes that affect patient care. This awareness is the key to noting risks and preventing them.*

Reluctance to simplify: *Simple processes are good, but simplistic explanations for why things work or fail are risky. Avoiding overly simple explanations of failure (unqualified staff, inadequate training, communication failure, etc.) is essential for understanding the true reasons patients are placed at risk.*

Preoccupation with failure: *When near-misses occur, these are viewed as evidence of systems that should be improved to reduce potential harm to patients. Rather than viewing near-misses as proof that the system has effective safeguards, they are viewed as symptomatic of areas in need of more attention.*

Deference to expertise: *If leaders and supervisors are not willing to listen and respond to the insights of staff who know how processes work and the risks patients face, you will not have a culture in which high reliability is possible.*

Resilience: *Leaders and staff need to be trained and prepared to know how to respond when system failures do occur.*

These thought processes should be implemented from the beginning and kept in play as case-mix complexity grows and new personnel are incorporated.

Biomedical Engineering Support

Pediatric cardiac care is heavily reliant upon equipment to safely carry out the procedures and care of children during and after the intervention. The level of technological sophistication that has been achieved in today's equipment provides us with safeguards previously unavailable. However, these features also come with significant costs, which few LMICs can afford. Moreover, although much of the improvement in hardware was healthcare professional driven, it is not essential to provide safe cardiac care to children. Adequate equipment that have been refurbished and certified for human use can be acquired at a fraction of the cost of a new one, and in many cases as developed countries' hospitals upgrade their equipment one can obtain the replaced equipment for shipping costs alone.

Our approach has been to provide critical pieces of needed equipment that have been refurbished but that are not so outdated that replacement parts or entire pieces cannot be found readily. The equipment is tested before it is shipped from the United States and an experienced biomedical engineer travels with the team's first trip to each country annually. Repairs are made on this first trip; equipment in need of replacement is identified and sought for between trips. We have used point-of-care testing as a means to bypass local laboratory deficiencies or inefficiencies. We routinely bring two hand-held point-of-care devices and a supply of necessary cartridges on all trips where we are knowledgeable of local laboratory shortcomings.

A Different Way of Doing Business

There are many issues confronting a team from a developed country visiting a center in an LMIC, which directly impact the decision to operate, subsequent patient care, and utilization of resources. Children in North America and Europe are now operated on mostly as newborns and infants and it is unusual to provide a primary operation on someone in late childhood or adolescence. The consequences of chronic congenital heart disease are apparent and given the paucity of resources available for extended or sophisticated care, special approaches need to be adopted to care safely for these children.

Chronic, pulmonary hypertension and polycythemia are just a few of the consequences of chronic congenital heart disease that the clinician faces and can impact results if approached as a child in a developed country. Pulmonary hypertension secondary to untreated L-to-R shunts is extremely common and nitric oxide and extracorporeal membrane oxygenating devices are nonexistent. We have modified our ventricular septal defect patch closure allowing for R-to-L shunting post-operatively should pulmonary hypertensive crises develop (Novick et al. 2005). Moreover, due to the ubiquitous presence of sildenafil, all patients demonstrating bidirectional shunting before the operation are treated for periods of days before the operation and continued in the immediate post-operative period for periods of 1 week to 3 months.

Malnutrition is common and infectious complications more common after surgery than in the developed world (Jenkins et al. 2014). To minimize post-operative nosocomial pneumonia, we pursue a program of fast track recovery in every

child operated upon. Just over 70% of the children we operate on are extubated in the first 4 h after arrival in the ICU (Shekerdemian et al. 2000). Our protocol for pain management in the immediate post-operative period of acetaminophen and ibuprofen helps us to facilitate early extubation with a very low rate of re-intubation.

Children requiring pulmonary ventricle to pulmonary artery valve conduits have few options in LMICs. The cost of a commercial valve conduit can be prohibitive unless funded by the government or donated by the visiting team. We have adopted the use of several unique materials to provide these children with options for commercial valve conduits including autologous pericardium, Polytetrafluoroethylene (PTFE) large-size conduits, and more recently de-cellularized intestinal submucosa scaffolding (Gilbert et al. 2011).

Development of a Teamwork Culture with Nurse Empowerment and a Horizontal Hierarchy

In our experience, when we start the process of developing a new assistance program in emerging countries, the more resisted changes to introduce are those that are viewed as traumatic changes in culture. This phenomenon is particularly evident in health centers located in countries where the decision-making authority is traditional and pyramidal. By this we mean, from top to bottom, from older to younger, from doctors to nurses, and from surgeon to everyone else in the group.

One of the pillars of our philosophy rests in the horizontalization of hierarchy. Our organization functions by allowing individuals to challenge and discuss any and all the options in the daily management of patients, independently of degrees, roles, and age, and based solely on experience. We try to convey and implement, when possible, a similar approach to problems in those programs under our assistance.

This philosophy of horizontal hierarchy is not limited to bedside clinical issues. We manage our organization in a similar way. While there are fixed roles and responsibilities within our organization, any and all issues are open for discussion and while a decision-making structure is in place, all voices are heard before making final decisions.

The empowerment of bedside nurses, operating room technicians, perfusionists, respiratory techs, etc. can be extremely helpful in the process of creating a culture where patient safety is paramount.

Data Collection

The collection of data on interventions is an important building block in the development of any pediatric cardiac program. Program growth and improvement cannot be measured unless data are gathered on each patient and analyzed on a quarterly/annual basis. We encourage all our affiliate programs to develop a local in-house database and to subscribe to one of the many international databases. We have maintained a comprehensive database on all operations performed during all our visits and have nearly 8000 primary operations archived to date.

There are several database registries available for use through the Society of Thoracic Surgery, the European Congenital Heart Surgeons Association, and The Asian Society of Thoracic Surgery. We, and others, have noted reluctance over the years for new programs to share their data with international registries secondary to reluctance to disclose surgical or interventional results that fall below international standards. As such, we embarked on an effort to create a database and registry with Boston Children's Hospital and the University of Geneva in 2007, which allows enrollment of programs only located in LMICs.

This initiative is the International Quality Improvement Collaborative in Pediatric Cardiac Surgery in Developing Countries (IQIC) and now has more than 30 institutions participating throughout the world. The IQIC is unique in that in addition to routine reporting of results of the group and individual institutions, it routinely provides webinars. The webinars are structured to improve specific aspects of the care of children with cardiac interventions. The first publication from the IQIC analyzed the results of the webinars on surgical site infections (Khan, Abdullah et al. 2017). To date, this service is provided without cost to the participants.

Data Monitoring

Although not a systemic part of our program assistance methodology, we believe real-time data monitoring is as important as data acquisition for the development of a solid cardiac surgery program. Outcomes data once entered into our database, must be brought to life by some type of data monitoring system that provides a current and dynamic view of the outcomes as they happen. This type of data management (data acquisition followed by data visualization) avoids the perils of looking retrospectively at the data and making the adjustments a year or 6 months after we realize a trend toward declining clinical outcomes has been occurring.

We favor the use of software such as the Variable Life-Adjusted Display (VLAD) currently used by the Society for Cardiothoracic Surgery in Great Britain and Ireland (Novick et al. 2008) to assess and present to the public the mortality of their cardiac surgery centers. This program, which was provided free of charge to us by the University College of London Operational Research Unit (Clinical Operational Research Unit n.d.), allows for real-time monitoring of binary variables based on an observed/expected calculation.

Table 1 shows data on the eight common outcomes quality measures (Jacobs et al. 2012) in 2709 of our surgeries carried out in 10 LMICs between January 2008 and June 2013. The difference in trends is self-evident. While our observed outcomes are better than expected (above the horizontal line) for five important quality measures (surgery for chylothorax, diaphragm plication, mediastinitis, need for a permanent pacemaker, and sepsis), we were trending below the expected results on two critical variables (take-back for bleeding and reoperation/revision during the same admission) (Cardarelli et al. 2014).

The visualization of the available data in our database allowed for a detailed analysis, utilizing the same software, of the countries where these two outcomes were lagging. For instance, after assigning an expected incidence of 0.031% to the "*take-back for bleeding*" events, we realized that our bleeding issues were not generalized but rather limited to five of the ten countries we were operating in (Figs. 2 and 3).

The main advantage of the use of this type of tool is the real-time visualization of a problem, since this graph can be actualized as soon as data on a new patient are added to the software running score sheet.

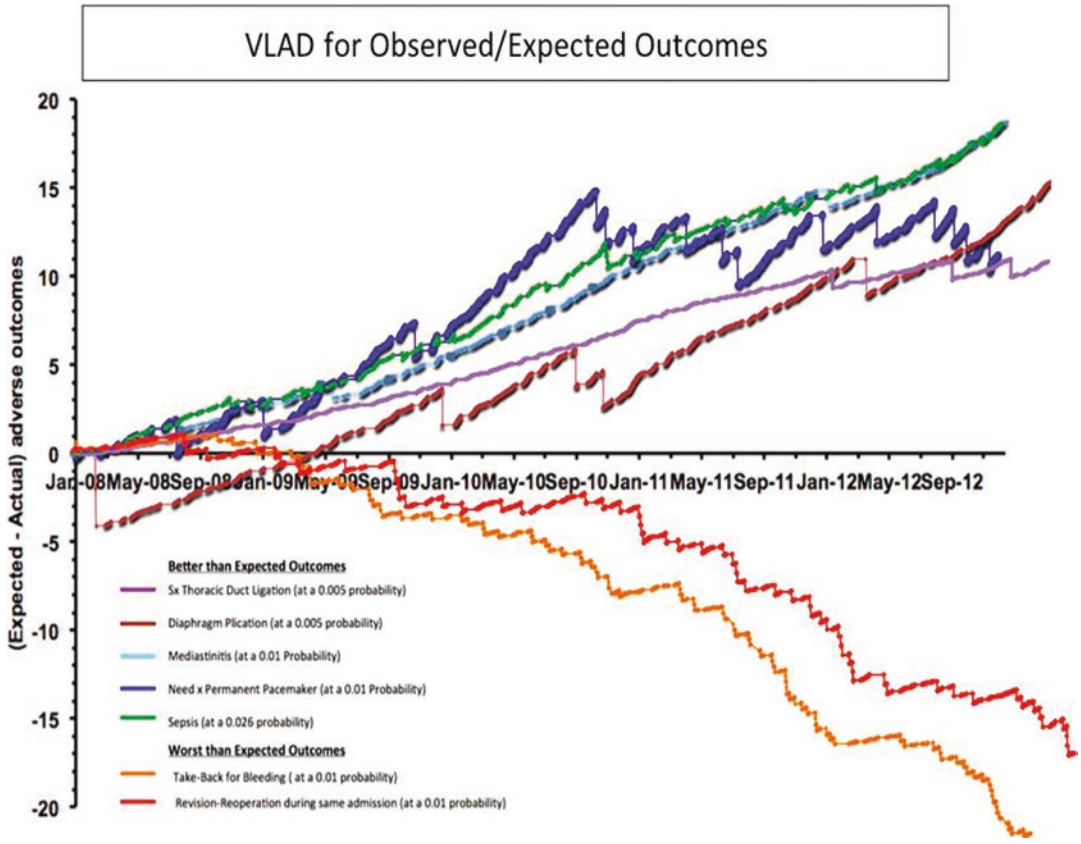

Fig. 2 A visualization of data collected on eight common quality measures over 4 years (January 2008–September 2012). Lines below the expected horizon (horizontal line) demonstrate worst than expected complications in the areas of take-back for bleeding and unexpected reoperation/revision during the same hospitalization

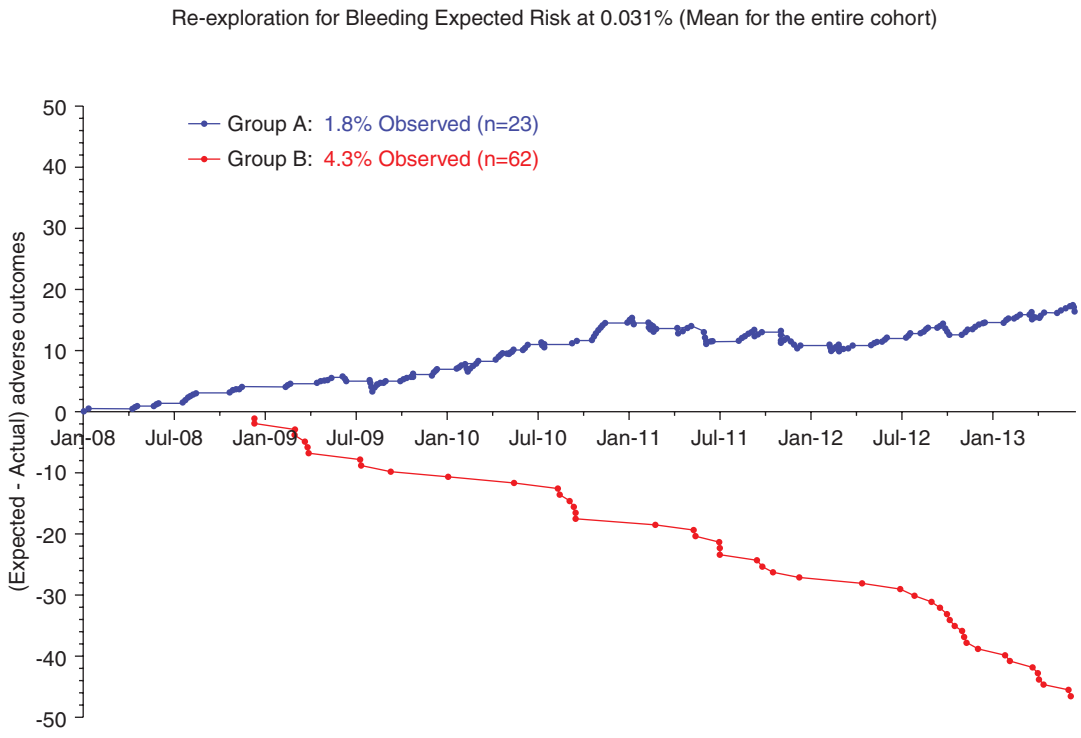

Fig. 3 Countries in group A had a better than expected frequency of surgical bleeding with an overall 1.8% rate. Meanwhile, countries in group B performed worst than expected with a take-back rate for bleeding of 4.3%

Summary

Despite enormous scientific progress in many areas of medicine and public health, even today a significant proportion of children born with congenital heart disease in Asia, Africa, and Latin America do not receive proper diagnosis or treatment.

The human toll has never been calculated and the economic burden of this unsatisfied demand for services is overwhelming but never before has been properly addressed. While in the short term this problem is unlikely to be solved, well-planned surgical/educational humanitarian campaigns combined with adequate locally budgeted resources and a sustainable plan may, in the long term, create the conditions by which most children born with heart defects in the developing world could be diagnosed and treated in time to have a full and productive life.

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Medical Education for Congenital Heart Disease

Amy M. Babb and Calvin Kuan

Abstract

Congenital heart disease (CHD) is a complex and evolving field of medicine that has led to increased survival and quality of life for many patients. This growing population of CHD patients requires a specialized team of cardiologists, intensivists, anesthesiologists, and surgeons to ensure satisfactory outcomes. Globally, there are very few physicians with specified training in congenital heart disease and even fewer training programs available to educate future specialists. Building quality education programs is paramount for future advancements in CHD and should be a key aspect in establishing any comprehensive program. This chapter will provide an understanding of the current established education pathways in pediatric and adult cardiology, intensive care unit (ICU), and anesthesiology and summarize some of the key components for building a CHD program.

Keywords

Education · Training · Congenital heart disease · Pediatric cardiac anesthesiology · Pediatric cardiac intensive care · Adult congenital heart disease

Introduction

Congenital heart disease (CHD) is one of the most common birth defects, affecting millions of children and adults throughout the world. The true incidence is difficult to know but is often cited between 8 and 12 per 1000 live births per year, with the Center for Disease Control reporting 1% incidence in the United States (Liu et al. 2019). These numbers likely underrepresent the true global impact of CHD. A recent worldwide assessment found the CHD incidence closer to 17/1000 live births, with an even higher incidence in select countries in Africa and Asia (Wu et al. 2020). It has also been observed that the overall prevalence of patients with CHD is increasing with an even larger increase in adults with CHD, who now account for more than half the CHD population in North America (Marelli et al. 2014). In addition, the overall global CHD mortality has decreased by more than 30% from 1990 to 2017 (GBD 2015 Disease and Injury Incidence and Prevalence Collaborators 2016; Wu et al. 2020). These trends show the phenom-

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enal medical and surgical advances in CHD as more patients with once fatal anomalies are now living longer and into adulthood. Unfortunately, there continue to be very limited CHD resources and many people continue to have almost no access to CHD specialists. It is estimated that to meet the needs of this growing population, 1 cardiac center performing between 300 and 500 CHD surgeries per year per 1–2 million people is needed (Vervoort et al. 2020). Unfortunately, this is far from reality with many countries without a single CHD center (Yacoub 2007). In addition, much of the world has less than two pediatric cardiac surgeons per million people, with some areas, like sub-Saharan Africa, as low as 0.08 per million (Vervoort et al. 2020).

In addition to congenital cardiac surgeons, cardiologists, anesthesiologists, and intensivists specializing in CHD are also essential to a center capable of caring for CHD patients. To develop a successful pediatric heart center, especially when looking from a global perspective, having training programs to teach and retain these subspecialty physicians is a key component. CHD medical and surgical specialties have evolved tremendously in the last few decades, but formalized training programs are still in the beginning stages. At present, there are limited standardized criteria for training, evaluation, or maintenance of competency in pediatric cardiac anesthesiology, pediatric cardiology, pediatric cardiac critical care, or adult congenital cardiology. The primary goal of this chapter is to help the reader understand the current CHD physician training paths under development and to understand what is needed to build a CHD training program. Examples of existing training programs in pediatric cardiology, adult congenital heart disease (ACHD), pediatric cardiac intensive care unit (CICU), and pediatric cardiac anesthesiology are included to highlight some of the key aspects of training in CHD. A brief discussion of the necessary components of a pediatric heart program will also be presented to provide a broad perspective on establishing training and education in CHD.

Pediatric Cardiac Anesthesiology Training

The field of pediatric cardiac anesthesiology is a unique and evolving medical subspecialty with high-level collaboration from cardiac surgery, cardiology, and critical care. The many advances in surgical and critical care necessitate the evolution of training for anesthesiologists caring for patients with congenital heart disease (CHD). In addition to the increased surgical complexity, more aspects of education are now necessary, such as advances in transesophageal echocardiography (TEE), vascular access techniques, and in-depth knowledge of CHD physiology and pharmacology.

Anesthesiologists are trained first in general adult perioperative care and then seek subspecialization through fellowship training as desired. Historically, anesthesiologists interested in pediatric cardiac anesthesia would then pursue mentorships or on-the-job training since formal programs did not exist. As the field of CHD continued to grow, large academic institutions began offering more structured training programs, but this was still individualized toward the perspective and case exposure at the specific centers (Shapiro and Reza 2021; Nasr et al. 2022a). Currently, societies, like the Congenital Cardiac Anesthesia Society (CCAS) and the European Association of Cardiothoracic Anesthesiology and Intensive Care (EACTAIC), are working to provide more specified prerequisites and detailed requirements for pediatric cardiac anesthesia education to ensure comprehensive training.

In the United States, the Accreditation Council for Graduate Medical Education (ACGME) defines postgraduate medical training for all major medical specialties. Training standardization helps provide a benchmark for the level and quality of trainee education. Recently, experts in the field of pediatric cardiac anesthesiology developed ACGME requirements for pediatric cardiac anesthesiology education. The ACGME uses core competencies and milestones to help programs develop an appropriate curriculum (Table 1).

Table 1 US ACGME Core Competencies as applied to pediatric cardiac anesthesiology (Nasr et al. 2018, 2022a, b)

ACGME six core competencies	PCV anesthesiology example
Patient care and procedural skills	Perioperative anesthetic skills and management of CHD patients
Medical knowledge	Understand CHD anatomy and physiology
System-based practice	Patient safety and quality improvement initiatives for CHD
Practice-based learning and improvement	Self-evaluation and lifelong learning
Professionalism	Professional and ethical behavior
Interpersonal and communication skills	Communication with patients, families, and staff

ACGME Accreditation Council for Graduate Medical Education, *CHD* congenital heart disease, *PCV* Pediatric cardiovascular

Emphasis is placed on ensuring each program has the appropriate resources (e.g., pediatric cardiac anesthesiology fellowship programs should have designated operating rooms) and requirements for the program director and faculty. In addition, the ACGME has specifications for feedback/evaluation of the program and the trainee.

Trainees in the United States must complete a specified anesthesiology training program followed by either a fellowship in pediatric or adult cardiac anesthesia. If the trainee pursues adult cardiac anesthesia, there is a 1-month requirement in pediatric anesthesia, preferably during the adult cardiac anesthesia fellowship. The ACGME fellowship in pediatric cardiac anesthesiology, formalized in 2021, is 12 months long, with 9 months of clinical care, 1 month of cardiac intensive care experience, and the remainder open to elective rotations. To gain appropriate exposure, a minimum of 100 cardiac surgeries on bypass, 50 where the fellow is the primary provider, is required. Table 1 lists the required cases within that 12-month interval. In addition to cardiac surgery cases, there are minimum requirements for interventional and diagnostic cardiac catheterization, electrophysiology, and imaging cases. Trainees must place at least 30 central venous catheters and 30 arterial lines. At the end of the 12-month duration, the trainee should have an appropriate knowledge base to provide safe clinical care. There is no formal mentorship upon completion of training, but many experts in the field agree that the 1-year fellowship does not make an expert; continued learning and mentoring are essential during the first years of independent practice. At the time of publication, there is no formalized post-training exam or board certification in pediatric cardiac anesthesiology (Nasr et al. 2018, 2022a, b).

The European Association of Cardiothoracic Anesthesiology and Intensive Care (EACTAIC) recently published the first edition of a recommended pediatric cardiac anesthesiology curriculum in 2021 (El-Tahan et al. 2022). A key difference between the ACGME and EACTAIC recommendations is the prerequisite education for pediatric cardiac anesthesiology. The EACTAIC requires 1 year of pediatric anesthesia and 1 year of adult cardiac anesthesia training before pursuing pediatric cardiac anesthesiology advanced training. The current recommendation is a 12-month program, including 1 month of critical care medicine and a minimum of 100 pediatric cardiac surgeries, with the majority performed with extracorporeal circulation, and 50 cardiac interventional cases. Table 2 lists the case requirements for both the United States and Europe. The EACTAIC has suggested 50% of cases be performed in children less than 4 years and 20% of cases younger than 1 month. There is no specific requirement for training in adult congenital heart disease, but it is encouraged. Similarly, the EACTAIC lists suggested technical skills and medical knowledge, including mandatory completion and passing of the theoretical portion of adult TEE certification. After completion of the 12-month training program, the trainee must submit the required materials (i.e., logbook, feedback, and evaluations) to be awarded certification in pediatric cardiac anesthesiology.

Many parts of the world do not have access to formalized pediatric cardiac surgery programs due to limitations in resources and the inability to train and sustain the specialists required for such organizations. Outside of high-income countries, very little formalized training in pediatric cardiac

Table 2 Comparison between ACGME and EACTAIC requirements for minimum case experience for pediatric cardiac anesthesiology training (Ross et al. 2015a; El-Tahan et al. 2022)

	ACGME	EACTAIC
Surgical cases with CPB		
Atrial septal defects/ ventricular septal defects/ atrioventricular septal defects/ Tetralogy of Fallot	20	**
Ventricular and/or atrial septal defect	**	15
Atrioventricular septal defects	**	10
Tetralogy of Fallot (TOF)	**	10
Left-sided valvular lesions	**	12
Bidirectional Glenn	5	5
Fontan procedure	4	5
Miscellaneous (e.g., Rastelli, Damus-Kaye-Stansel, intracardiac tumors)	**	2
Neonatal procedures truncus, arteriosus, Total anomalous pulmonary venous return	3	**
Procedures in Hypoplastic Left Heart Syndrome	3	**
Valvular lesions	20	**
Transposition of Great Arteries (TGA)	3	**
Transplant (heart or lung) or Ventricular assist devices, Extracorporeal Membrane Oxygenation, Intra-aortic balloon pump	1	**
Palliative shunt	1	**
Surgical cases without cardio-pulmonary bypass		
Modified Blalock-Taussig shunts	**	5
Coarctation repair	3	5
Pulmonary artery banding	**	5
Patent ductus arteriosus closure	3	2
Treatment of vascular ring	2	1
Cardiac percutaneous intervention procedures		
Diagnostic	20	10
Interventional	25	**
Neonatal aortic and/or pulmonary vessel or valve treatment (e.g., Pulmonary artery stenosis, coarctation)	**	5
Atrial septal defect/ventricular septal defect/ patent ductus arteriosus device closure	**	20
Other therapeutic	**	15
Electrophysiology studies	10	5

**Number not specified

anesthesiology exists and few publications discuss anesthesia specific to low- and middle-income countries. One recent article describes an experience working with existing pediatric cardiac programs throughout the world, using the resources already in place, to help educate and simplify the anesthetic challenges with CHD cases (Cvetkovic 2018). Limiting case complexity to fit the resources available was emphasized to decrease morbidity and mortality. In addition, local teams were taught to use regional anesthesia and tailor the anesthetic for fast-track or in operating room extubation (Cvetkovic 2018). Because of the heterogeneity of resources for each pediatric cardiac surgical program worldwide, the training for CHD anesthesiologists may not be as formalized as in the United States or Europe. Using the previously mentioned published guidelines, a global perspective could provide a futuristic curriculum in pediatric cardiac anesthesiology.

Pediatric Cardiology

Since the world first reported successful surgery for congenital heart disease in Boston on August 26, 1938, by Dr. Robert E. Gross—ligation of a patent ductus arteriosus in a 7-year-old girl (Noonan 2004; Alexi-Meskishvili and Böttcher 2010)—the discipline of pediatric cardiology emerged with the realization that congenital heart conditions could be surgically treated. Shortly thereafter, Helen Taussig, considered the mother of pediatric cardiology, started training pediatricians in Baltimore, MD, to care for patients with CHD, and in the 1950s, training programs in pediatric cardiology were developed in Boston, Cincinnati, Toronto, Europe, and other parts of the world (Noonan 2004; Alexi-Meskishvili and Böttcher 2010).

In most countries around the world, training to become a pediatric cardiologist requires 6–8 years after medical school. To ensure a solid foundation in medical knowledge and familiarity with the care of infants and children, all programs require some formal training in general pediatrics.

In 2020, the Association for European Paediatric and Congenital Cardiology (AEPC) (Heying et al. 2020) published an official position paper with recommendations for the mini-

mum requirements for training to be recognized as a pediatric and congenital cardiologist, which is the title chosen for the specialist to emphasize the fact that the care encompasses patients from the fetus through adulthood. The prerequisite for training in pediatric and congenital cardiology is a minimum of 3 years of training in general pediatrics and must include at least 6 months of neonatal and pediatric intensive care. Requirements specified during this training include a minimum of 3 months of adult CHD care and other procedures listed in Table 3. Trainees are required to maintain a logbook to document cases and procedures throughout their training, along with verification of the logbook by their supervisor. Involvement in academic endeavors including a research project, attendance at conferences, and publications or presentations is required. Finally, to complete certification, there must be a final assessment.

Training for pediatric cardiology in the United States follows a similar path to that in Europe. Prerequisite training is the completion of a 3-year general pediatrics residency (the term given to the postgraduate education in a specific specialty). The trainee may then enter a 3-year pediatric cardiology fellowship (the term given to a training program that follows a residency). Core requirements for pediatric cardiology fellows (Ross et al. 2015a; Nasr et al. 2018, 2022a) in the United States were previously based on a prescribed minimum number of months in specific pediatric cardiology areas of care: for example, 4–6 months of echocardiography, 2–4 months of cardiac intensive care. A 2015 update of the training guidelines reflected a paradigm shift in medical education and now requires competency-based training for fellows (Ross et al. 2015a, b; Nasr et al. 2018, 2022a; Dabbagh et al. 2021). A set amount of time on specified rotations and performing a specified minimum number of procedures are suggested but are not sufficient to qualify for certification. These minimum numbers are used for assessment of skill, but not necessarily enough to ensure competency. Built into the 3 years of fellowship are 12–18 months for scholarly activity (see Table 3).

Advanced 2nd-year fellowships following pediatric cardiology fellowship are available for those who seek to further subspecialize within pediatric cardiology (e.g., interventional cardiac catheterization). These programs may choose to develop their curriculum that exceeds the basic core competencies and/or meets advanced competencies. However, as the field of pediatric cardiology becomes more and more specialized, it is becoming more common for fellows to seek an additional year of advanced fellowship training to become subspecialized especially in academic centers.

Pediatric cardiology training in the United Kingdom (see Table 4) is distinct from other European countries in that the training period is at least 5 years (ST4–8) after 3 years of general pediatrics training (ST1–3) and 2 Foundation years that occur immediately after medical school. This longer duration includes 3 core years and 2 years in an area of special interest (e.g., electrophysiology, heart failure/transplantation). These last 2 years would be considered the equivalent of the "4th year" advanced fellowship sub-subspecialty training in the United States. Alternatively, physicians could enter the pathway after 2 years of core adult internal medicine (IM) if they complete at least 1 year of core pediatrics with a minimum of 6 months of neonatology. It is worth noting that pediatric cardiology is an accredited specialty on its own in the United Kingdom, as opposed to most other countries where it is considered a subspecialty within pediatrics. Trainees in the United Kingdom are not required to meet the AEPC requirements for the training described above. In recent years the Shape of Training review (a national initiative in the United Kingdom) is gradually reforming postgraduate medical education and training. One of the changes is changing the term "competence" to "capability" to emphasize the fact that graduating trainees need to have the ability to independently manage complex situations, as opposed to having checked off boxes demonstrating completion of a finite list of procedures, skills, and knowledge (McMahon et al. 2022).

Table 3 Comparision between US and European requirements for training in pediatric cardiology

Pediatric cardiology training	United States (Ross et al. 2015a; Nasr et al. 2018, 2022a)	Association for European Paediatric and Congenital Cardiology (AEPC) (Heying et al. 2020)
Year most recent recommendations published	2020	2020
Duration of training	3 years of pediatric cardiology (with a minimum of 12 months of clinical experience)	3 years of pediatric cardiology depending on background training
Prerequisite training	3 years of general pediatrics	3 years of general pediatrics (must include 6 months in neonatal/ pediatric intensive care)
Outpatient case management	NA	200 patients
Inpatient case management	NA	200 patients
ICU patients	Minimum 2 months if front line provider Minimum 4 months if consultant role	50 patients
Cardiac catheterization (including balloon atrial septostomy)	50 cases as an active participant to catheterization attending	50 cases
Cardioversion	4	5
Fetal echocardiography	Not required to perform or interpret without advanced training	20 observed
Transesophageal exams	Not expected to be able to perform or interpret without advanced training	50 total/25 primary operator
Transthoracic exams	150 perform and interpret 100 review and interpret	500 total/300 supervised With a minimum of 400 with pathology
Electrocardiograms interpreted	500	150
Postoperative epicardial wire/ esophageal study	5	
Electrophysiologic study cases	Diagnostic study 10 Ablation 5	10
Exercise tests	10	50
Holter monitors	50	50
Imaging: interpret chest X-ray	NA	100
Interpret MRI, CT, nuclear medicine study	Not required to interpret without advanced training	10 total
Pacemaker: observe implantation	NA	5
Participate in PM testing function	NA	20
Primary operator PM testing	20	20
Pericardial aspiration under the supervision and demonstrate proficiency as operator	NA	Total 2
Adult CHD rotation	NA	Minimum 3 months
Adult CHD patients managed	NA	50
Require completion of logbook	Log of procedures only	Yes
Assessment of competency	Yes, and board certification examination	Yes, throughout training

CHD congenital heart disease, *CT* computed tomography, *ICU* intensive care unit, *MRI* magnetic resonance imaging, *NA* not available, *PM* pacemaker

Table 4 Requirements for training in paediatric cardiology in the UK

Pediatric cardiology training	United Kingdom (McMahon et al. 2022)
Year most recent recommendations published	2021
Duration of training	Minimum 5 years (ST4–8), and depends on the achievement of training competencies
Prerequisite training	(a) 2 years of foundation training + (b) 3 years of core pediatrics (ST1–3) + 5 years of pediatric cardiology (ST4–8) (c) 2 years of internal medicine (CT1–2) + 1 year of core pediatrics/neonatal training (ST1)
Assessment of competency	Yes, Knowledge-Based Assessment (KBA); EACVI certification optional

ST1-3 first three years of basic specialty training, *ST4-8* subsequent five years of higher specialist training, *CT1-2* core trainee years 1-2, *EACVI* european association of cardiovascular imaging

Pediatric Cardiac Critical Care

Early intraoperative management of the child undergoing cardiac surgery consisted of hand-ventilation in the operating room by the anesthesiologist and extubating on the table at the end of the procedure. Children were placed in an oxygen tent on the ward. There were no ventilators, invasive monitors, or intravenous infusions for pediatric patients in the 1950s (Checchia et al. 2005, 2021). The first intensive care unit (ICU) was established in Copenhagen in 1953 to allow more efficient nursing care of large numbers of polio patients in iron lungs. The first pediatric intensive care unit (PICU) in the world was opened by Gilbert Huault in 1962 in France (Parker et al. 2021). Historically, both adult and pediatric ICUs were developed from postoperative recovery rooms by anesthesiologists. Improvements in mechanical ventilation and monitoring permitted anesthesiologists to care for patients during more complex operations leading to more patients needing somewhere to recover postoperatively. In the 1970s, additional advances in surgical techniques, medical technologies, and therapies (e.g., prostaglandin, echocardiography, interventional cardiac catheterization) stimulated the evolution of the care of the child with congenital heart disease, eventually resulting in the development of the specialty of pediatric cardiac critical care.

The first pediatric cardiac intensive care units (CICUs) in the United States were established in Boston and Minneapolis in the late 1960s (Parker et al. 2021). However, in the subsequent decades, most pediatric cardiac patients were cared for in mixed PICUs/CICUs by pediatric intensivists until dedicated CICUs became more common in the 1980s and 90s. According to the most recent data from 2020 (Horak et al. 2020), there are now 120 intensive care units in the United States caring for pediatric cardiac patients. Of these, 61 (51%) are considered mixed ICUs and 59 (49%) are considered dedicated CICUs. Of interest is that 13 (23%) of CICUs reported that they sent patients to the PICU after cardiac surgery (Horak et al. 2020).

In terms of physicians who staff the ICUs in the United States, the most common background training is via pediatric critical care medicine (PCCM). This is true for both mixed PICUs/CICUs (98% of attendings were PCCM trained) and dedicated CICUs (63% of attendings were PCCM trained) (Horak et al. 2020). In the last two decades, there has been an increase in CICUs—from 21 in 2001 up to 55 in 2021 (Checchia et al. 2005, 2021)—and alongside this growth, there has been a shift to having physicians trained in pediatric cardiac critical care managing these units.

In 2011, the Association for European Paediatric Cardiology first proposed recommendations for physicians interested in pursuing a specialization in pediatric cardiac intensive care (da Cruz et al. 2011) (see Table 5). Though not explicitly stated in the document, trainees presumably must first complete training in general pediatrics and be in a pediatric cardiology fellowship. Subsequently, trainees specializing in pediatric cardiac critical care must complete at least 1 year of pediatric cardiology and 3–6 months of

Table 5 Comparison between US and European requirements for training in pediatric cardiac critical care (da Cruz et al. 2011; Feltes et al. 2015; Tabbutt et al. 2022)

Pediatric cardiac critical care training	United States	Association for European Paediatric and Congenital Cardiology (AEPC)
Duration of training	1 year after a primary fellowship in pediatric cardiology or critical care; 2 years for dual training in the second specialty	Level 1: 6 months (required for all pediatric cardiology trainees) Level 2: 9 months (optional) Level 3: 12 months on top of level 2 training (optional)
Prerequisite training	3 years of general pediatrics training, and 3 years of pediatric cardiology *or* 3 years of pediatric critical care	1-year pediatric cardiology; 2–6 months of neonatal intensive care (as required for general pediatric cardiology training)
Institutionally required minimums		
Number of CPB cases per year	250 per year (averaged over 5 years)	Levels 1 and 2: >100/year Level 3: >150/year
Minimum STS STAT 5 cases	10 STS STAT 5 cases per year (averaged over 5 years)	
Number of neonatal (<28 days) cases per year	35	
ECMO program	Required	
VAD program	Required	
Dedicated CICU	Required	
Participation in data registries	Required: STS or PCCCC data registries	Required: EACTS-STS and Aristotle score
At least one PCCC faculty must have completed 4th year training, is dual boarded, or has over 10 years of experience in practice	Required	NA
The institution must have categorical PCCM and pediatrics cardiology fellowship	Required	NA
Research requirement	Optional	NA
Adults with CHD experience/rotation	Optional	NA
Support of leadership	Required	
Assessment of competency		Logbook and certification by supervisors, not only based on a minimum number of cases

CHD congenital heart disease, *CICU* cardiac intensive care unit, *CPB* cardiopulmonary bypass, *EACTS* european association of cardio-thoracic surgery, *ECMO* extracorporeal membrane oxygenation, *NA* not available, *PCCC* pediatric cardiac critical care, *PCCCC* pediatric cardiac critical care consortium, *PCCM* pediatric critical care medicine, *STAT* Society of thoracic surgeons- european association for cardio-thoracic surgery, *STS* society of thoracic surgeons, *VAD* ventricular assist device

neonatal intensive care. Thereafter, three levels of training will be available.

Level 1 (basic) is the training required for someone to become a general pediatric cardiologist in Europe. All pediatric cardiology trainees must complete 6 months of intensive care experience and achieve basic understanding of issues for critical medical and surgical pediatric cardiac patients.

Level 2 (intermediate) is the training required for the pediatric cardiologist to become more

independent and develop more procedural skills. The minimum training period for this level is 9 months during the pediatric cardiology training period.

Level 3 (advanced) requires a minimum of 12 months, which can only occur after completion of full training in pediatric cardiology, and completion of Level 2. This is required to become pediatric cardiac intensivists who can independently manage all complex pediatric cardiac patients (da Cruz et al. 2011).

As with the AEPC guidelines for pediatric cardiology training, trainees in pediatric cardiac critical care must keep a logbook and meet with program directors every 3 months to confirm the development of skills and to certify competency after training.

On the other side of the Atlantic in the United States, there have been three pathways for physicians seeking such training; all require completion of a residency in general pediatrics. The first is the completion of a fellowship in pediatric cardiology (3 years) followed by an advanced fellowship in pediatric cardiac critical care (1 year). The second is the completion of a fellowship in pediatric critical care (3 years) followed by an advanced fellowship in pediatric cardiac critical care (1 year). The third is dual training in both pediatric cardiology and pediatric critical care medicine for a total of 5 years. Trainees complete the first fellowship (e.g., either pediatric cardiology or critical care medicine) in the typical 3 years, then continue with the second fellowship in the other discipline that can be condensed into 2 years with permission. Requirements for training were proposed by a task force of the Pediatric Cardiac Intensive Care Society to establish an official subspecialty through the Accreditation Council for Graduate Medical Education (ACGME) and the American Board of Pediatrics (ABP) that oversee certification of pediatric specialties (Tabbutt et al. 2022). These requirements include recommendations for specific rotations (e.g., CICU, OR/anesthesia, catheterization lab, echocardiography), and learning objective topics (see http://links.lww.com/PCC/B866). Of note, training in Adult Congenital Heart Disease and dedicated research were both determined to be optional as a significant number of programs could not offer these experiences (Tabbutt et al. 2022).

ACHD Training

The face of congenital heart disease is evolving from primarily a pediatric disorder to complex adult comorbidity. It is estimated that in high-income countries, 90% of children with congenital heart disease will survive to adulthood (Moons et al. 2021). Although these numbers are likely not as optimistic in middle- and low-income countries, it is expected that with the advances in surgical palliation, more children worldwide will become adults living with congenital heart disease. In addition, 10–20% of all CHD surgeries are being performed on adults (Lei Lei and Heggie 2021) and the surgical and medical complexity is only increasing. Because of the advanced level of care needed, it is not surprising that ACHD patients cared for at specialized centers have had better outcomes (Mylotte et al. 2014).

As the volume and complexity of care of ACHD patients continue to increase, there is a growing need for specialists in the field. There is limited access to pediatric CHD specialists, so it is not surprising that globally there are even fewer physicians comfortable with managing adults with CHD. Pediatric cardiologists may not be universally comfortable with the comorbidities associated with aging and adult cardiologists are not formally trained in congenital heart disease. Because of this gap, additional training in adult congenital heart disease has been recommended to meet the need of this vulnerable growing population.

Globally, there are limited options for training in ACHD. A recent report on the current state of ACHD care in central and southeastern Europe

says there are no training programs in ACHD in this region (Brida and Gatzoulis 2019; Brida et al. 2021). The International Society of Adult Congenital Heart Disease (ISACHD) lists the available clinical fellowships by country, which include positions in the United States, Canada, Japan, Australia, Germany, the Netherlands, and the United Kingdom. Most of these positions are listed as 1 or 2 years in length and it is common for available spots to be left unfilled (Brida et al. 2021).

In the United States, the ACHD fellowship is 24 months long and there are different prerequisite pathways for trainees to pursue this advanced knowledge (Cedars 2016; Chowdhury et al. 2021; Kay and Moe 2021). The first is to complete 3 years of internal medicine residency followed by 3 years of adult cardiology fellowship. The second is the completion of a 3-year residency in pediatrics followed by a 3-year fellowship in pediatric cardiology and, finally, the third option is a 4-year combined internal medicine/pediatric residency followed by a 3-year pediatric cardiology fellowship. Regardless of the path, it is a sizable time commitment to pursue qualifications in ACHD in the United States. Within the ACGME accredited fellowship, there is a requirement to care for 200 hospitalized and 350 ambulatory care ACHD patients. Fellows spend 9 months of inpatient/consult care, 3 months of imaging, 2 months of cardiac catheterization, and 1 month in ICU to fulfill the requirements of training (Cedars 2016; Chowdhury et al. 2021; Kay and Moe 2021). For individuals trained in adult cardiology, there is a required 3 months of pediatric-focused rotations. Individuals trained in pediatrics/pediatric cardiology must complete 3 months of internal medicine and 3 months of adult cardiology. Combined IM/Pediatrics/pediatric cardiology graduates must complete 3 months of adult and adult cardiac-focused rotations. Upon completion of the 2-year program, trainees are then Board eligible and must pass a board certification exam.

In 2014, the European Society of Cardiology (ESC) published recommendations for the organization of care and training in ACHD (Baumgartner et al. 2014). Within this paper are expert recommendations for establishing a specialized center and training program for grown-ups with CHD. The consensus is that a training program should be of 24 months, with 18 months at a specialized center for adult CHD. For adult cardiologists, there is a 6-month requirement in pediatric cardiology and for pediatric cardiologists, 6 months of adult cardiology is required. The trainee is expected to gain sufficient knowledge in the full spectrum of CHD at the specialized center. It is recommended that they have participated in the care of >400 outpatients and >200 inpatients with CHD. Utilization and training in various imaging modalities are emphasized, with a requirement of >250 transthoracic echocardiographies (TTEs) and >50 TEEs performed, >50 interpreted cardiac MRI/CTs, >30 interpreted catheterizations, >20 catheterization participation, and >5 electrophysiology studies. Formal certification is suggested with the submission of a logbook and examination. Although these are not formalized training requirements to practice in Europe, they help solidify what type of training an ACHD specialist should have. Table 6 gives a comparative look at published requirements for ACHD training.

The United Kingdom (UK) has a designated path for further specialization in ACHD (Crossland et al. 2021). The current structure is divided into three levels of expertise (Brida et al. 2021). Training in ACHD is part of the core curriculum in adult cardiology training, so all adult cardiologists receive a basic level of training. If the trainee wishes to pursue additional experience, there is a 2-year subspecialization pathway that will provide the highest level of expertise available. A third option allows flexibility to further knowledge in ACHD through an additional year of ACHD training, but also allows the individual to pursue 1 year in a different subspecialty, like advanced imaging.

The United Kingdom has also categorized ACHD centers based on the level of available care (Report of the British Cardiac Society Working Party 2002; Crossland et al. 2021). A Level 1 ACHD center can provide the full spectrum of surgical, interventional, and medical

Table 6 Comparison between US versus proposed ESC recommendations for training in adult congenital heart disease (Cedars 2016; Chowdhury et al. 2021; Kay and Moe 2021; Moons et al. 2021)

	ACGME	ESC recommendations
Prerequisite training	• 3 years IM + 3 years adult cardiology *or* • 3 years pediatrics + 3 years pediatric cardiology *or* • Combined 4 years IM/pediatrics + 3 years pediatric cardiology	• Adult cardiology training, *or* • Pediatric cardiology training
Length of training	24 months	24 months
Minimum number of inpatient cases	200	200
Minimum number of outpatient cases	350	400
Required rotations	9 months inpatient/consults 1 month ICU 3 months imaging (echo, MRI/CT) 2 months catheterization lab	18 months at a specialized center for ACHD
Required procedures	No specific minimum procedure requirements Direct supervision of any procedure until acquired proficiency	250 TTEs 50 TEEs 50 cardiac MRI/CT scans Cardiac catheterizations (30 interpreted, 20 participated) 5 electrophysiology studies
Board certification	Yes	No; suggested having a logbook and exam

ACGME Accreditation Council for Graduate Medical Education, *ACHD* adult congenital heart disease, *CT* computed tomography, *ESC* European Society of Cardiology, *ICU* intensive care unit, *IM* internal medicine, *MRI* magnetic resonance imaging, *TTE* transthoracic echocardiography, *TEE* transesophageal echocardiography

care. A Level 2 center can provide comprehensive medical care, but invasive procedures are not offered. Level 3 is similar to a local center, providing care to fewer complex patients. It should also be emphasized that a well-developed training program cannot be built without an available comprehensive ACHD center (Baumgartner et al. 2014). Specifically, with suggested case and imaging requirements, the program must provide this opportunity. In addition, having various training programs is vital to the establishment and success of any heart center.

Specialty Certification

In considering the merits of whether to establish official national certification for a given specialty and mandate that all physicians training in that specialty pass the certification, each country must weigh the costs and benefits.

Arguments for mandating a certification process/certificate:

1. Patients and their families deserve to have some ability to gauge the quality of care they may receive for their loved ones going for cardiac surgery.
2. Physicians deserve some recognition for their years of hard work and study.
3. Hospitals and other countries may be able to rely on the certification to be reassured that if they recruit a physician from another region or country (e.g., for an underserved area) that physician has a reliable level of competency.
4. Internationally recognized certification could improve international job mobility.

Arguments against mandating a certification process/certificate (Anand et al. 2016):

1. There are no data that demonstrate that board certification leads to improved clinical outcomes.
2. There is a significant cost associated with studying for and taking board certification exams.

3. One question that must be asked is whether the certification will be required to practice in a given setting. In regions with limited human resources or staffing shortages, hiring only physicians with board certification could limit access to care.
4. Internationally recognized certification could result in a so-called brain drain where trained specialists leave lower-resourced countries for higher-resourced ones for higher income.

Certainly, high-quality patient care should be the goal and specialty certification could have a role. Establishing and maintaining a certification process will have to depend on buy-in from governments, hospital administrators, and physicians themselves as it requires a significant investment of time, effort, and money.

Considerations for an Effective Medical Education Program for Congenital Heart Disease

To design an effective medical education program for specialists in congenital heart disease, it is important to understand that the perioperative care of the child or adult with the congenital cardiac disease requires the coordinated efforts of an entire team with each member contributing specialized knowledge and clinical expertise. Initially, the neonatologist, primary care pediatrician, or pediatric cardiologist diagnose the lesion and refer the patient for surgery. Next, the surgeon repairs the lesion with the OR team, which includes the pediatric cardiac anesthesiologist, perfusionist, and operating room nurses. Third, intensivists and nurses in the cardiac intensive care unit care for the patient during the immediate postoperative period. Last but equally important are the specialists who act as consultants when unexpected issues occur (e.g., acute renal failure, intracranial hemorrhage), and other health care professionals who help in the recovery process (e.g., respiratory therapist, physical therapist, social worker) (see Fig. 1).

Historically, medical education was more of an apprenticeship with "See one, do one, teach one" as the prevailing doctrine. This method is not appropriate with the child with complex CHD. The ability to manage these challenging patients requires expert technical skills, significant depth of knowledge, and sophisticated clinical judgment that can only come with repeated exposure and deliberate practice. Acquisition of these skills, knowledge, and judgment cannot be accomplished only by reading a book or listening to a lecture. Learners may get a sense of how to

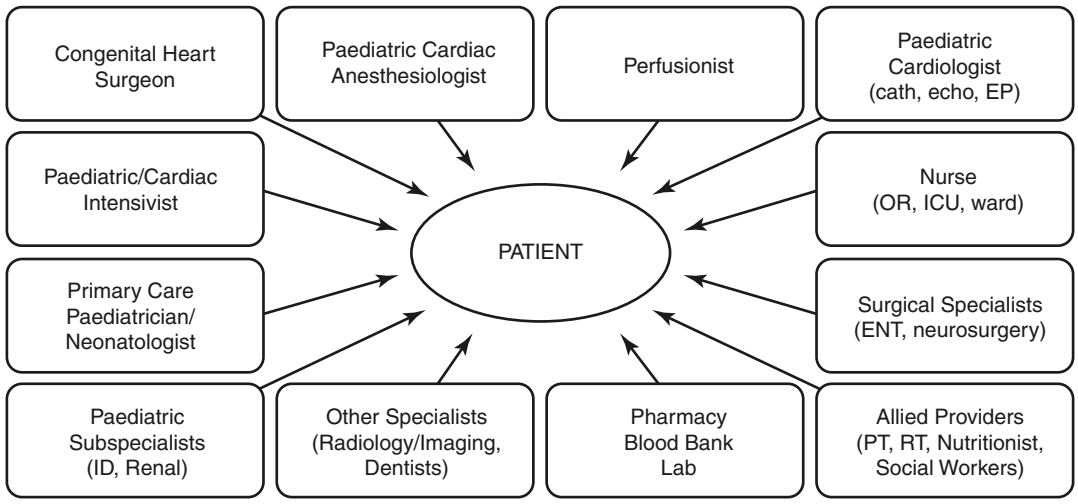

Fig. 1 Care of the patient with congenital heart disease requires cooperation of a multidisciplinary team from diagnosis to treatment to recovery. Figure created by Shannon Douglas Schwartz

place an arterial line by watching a YouTube video, but hands-on training and practice are required to achieve success. With interdisciplinary collaboration necessary to care for the complex CHD patients in challenging clinical situations, all members of the medical team must have a deeper understanding of all the issues rather than just following protocols and guidelines. This deeper understanding can only come with actual bedside clinical experience (i.e., number, type, and complexity of cases) and well-rounded training.

Case Volume

To support a training program for any of the specialists, a heart center must have an adequate case volume to ensure adequate exposure for the trainees and maintenance of skill for the staff. Hospitals developing teaching programs should understand what numbers of cases and personnel would be needed to achieve a critical mass such that education versus service needs are balanced, and outcomes are optimized. The optimal case volumes for a high-functioning heart center should be comparable to the optimal numbers for a teaching program.

There are ample data to show that case volume is directly associated with overall patient outcomes (Backer et al. 2020; Pasquali et al. 2020). Studies in the United States have shown that heart centers with an annual case volume of over 200–300 cases per year have better survival rates for their patients (Welke et al. 2009). In a 2015 survey of congenital heart surgeons in the United States, 14% of respondents felt that at least 50 CHD surgeries were required to maintain skills and expertise, 48% felt that at least 100 surgeries were required, and 31% stated that 150 surgeries should be the minimum (Morales et al. 2017). The relative importance of surgeon experience and case numbers versus that of the entire institution (e.g., anesthesiologists and ICU) may be difficult to determine though. For example, a study examining the outcomes after the Norwood procedure in patients with hypoplastic left heart syndrome demonstrated that survival is associated with institutional Norwood procedure volume, but not with individual surgeon case volume (Checchia et al. 2005, 2021). These results clearly show the impact of a team approach with complex CHD patients.

The European Association of Cardio-Thoracic Surgery (EACTS) proposed an optimal structure for a congenital heart surgery program in Europe consistent with the aforementioned numbers (Daenen et al. 2003). A single program should operate on at least 250 patients per year, representing a draining area of approximately 4–6 million people. This is consistent with suggestions from the United States for one heart center for every 4.6 million people, and Sweden and the United Kingdom where there is approximately one center for every 4.5–5 million people (Backer et al. 2020). Additional recommendations from the EACTS include a minimum of 100 neonate/infant cases per year.

Types of Cases/Types of Lesions

Closely related to case volumes are the types of cases needed to sustain a congenital heart center. For trainees to attain a well-rounded education, whether in the operating theater, intensive care unit, or clinic, the heart center should provide the opportunity for them to care for the entire spectrum of congenital heart disease. In smaller centers or countries with regionalized resources, when trainees are not able to obtain the necessary exposure in one center, they should be allowed to rotate to another center to gain appropriate experience.

A more judicious option for new heart centers may be to partner with more established programs that can provide mentorship and clinical support through the incubating process. The newer program can choose to carefully select cases with a lower risk of morbidity/mortality to treat in the early years while triaging more complicated and riskier cases to the "parent" program to be handled by senior surgeons, anesthesiologists, and cardiologists. Then, as the younger program gains confidence and experience, they can keep more and more patients. This approach has been suc-

cessful in less-resourced regions or regions with new population growth in high-income countries and low- and middle-income countries (Mainwaring et al. 2008; Bastero et al. 2017).

Resources: Human and Teams

The following is a brief overview of the necessary personnel needed to operate a heart center. These teams and resources help contribute to quality education programs in developing centers.

1. Surgeons: The European Association of Cardio-Thoracic Surgery suggests that each full-time congenital heart surgeon perform 125 operations per year—approximately 3 cases per week. To achieve full-time coverage and maintain a reasonable work–life balance, it is recommended that there should be at least two to three surgeons for each center (Daenen et al. 2003). This is consistent with the survey of US cardiothoracic surgeons, which found that the median number of practicing surgeons in a program was three (range of 1–8) (Morales et al. 2017).
2. Anesthesiologists: In the United States, the number of pediatric anesthesiologists in each program was comparable to the number of surgeons. The median number of pediatric anesthesiologists working with each surgeon was four (range from 0 to 14) (Morales et al. 2017).
3. Cardiologists: In the United States, the median number of pediatric cardiologists in each program was 12 (range of 3–72) (Morales et al. 2017).

In addition to the principal specialists, a host of other medical specialists, medical professionals, and support staff care for the patient with CHD and provide a well-rounded training experience for learners.

1. Physicians:
   (a) Pediatric medical specialists (e.g., neonatology, geneticist, pulmonology, neurology, infectious disease, hematology, GI, hematology/oncology, nephrology)
   (b) Adult cardiologist with CHD experience
   (c) Surgical specialists (e.g., ENT, neurosurgery, general surgery)
   (d) Other medical specialists (e.g., radiologist, pathologist, transfusion medicine, child psychologist)
2. Operating room staff: pediatric cardiac operating room nurse, pediatric perfusionist
3. ICU staff: pediatric cardiac ICU nurse, respiratory therapist
4. Cardiology staff: echocardiography tech, EKG tech
5. Hospital staff: pharmacist, transfusion medicine tech, laboratory tech, radiology tech, nuclear medicine tech, physical therapist, social worker, chaplain, child life specialist, physical therapist, speech/language therapist

Resources: Facility and Equipment

In addition to personnel, specific facilities must be available to care for the many medical needs of CHD patients. The European Association of Cardio-Thoracic Surgery recommends a dedicated pediatric cardiac intensive care unit for all centers to ensure adequate expertise from the staff (Daenen et al. 2003) as opposed to sharing space and personnel with adult services or non-cardiac pediatric services. The number of CICU beds required would be 6–8 beds for every 250 operations per year. In terms of downstream ward beds, the recommendation is for 10–12 ward beds for every 250 operations per year. Listed below are other examples of resources necessary in a heart center. This list may serve as a guide but must be tailored to the needs of individual centers.

Facilities that should be available for a full-service heart center include:

1. Operating rooms
2. Cardiac catheterization room
3. Electrophysiologic studies room
4. Cardiac ICU or pediatric ICU with cardiac experience
5. Pediatric ward and/or step-down unit
6. Neonatal ICU

7. Radiology/imaging services—CT, MRI, nuclear medicine
8. Ambulatory clinics for primary care, consultation, and follow-up care
9. Pharmacy
10. Medical laboratory
11. Transfusion services/blood bank
12. Transport services to retrieve patients from outlying locations

Educational Strategies

Be Humble and Know Your Limits

What may already be evident for those established in medicine is that the amount of medical knowledge and the pace of the expansion have exploded in the last half-century. In 1950, it was estimated that it would take 50 years to double the amount of medical knowledge. In 1980, the doubling time was estimated to be 7 years, while in 2020, it was projected to be just 0.2 years (Densen 2011). Medical students and physician trainees are expected to learn more and more in training programs that have not increased in duration. Physicians in practice have an even more difficult job keeping up with the growth of information while providing clinical care and teaching. Therefore, medical professionals must be humble and acknowledge that no one person can know everything or do everything (Anand et al. 2016). Even more importantly, care for complex patients requires a multidisciplinary team approach, so training must include not only knowledge, but also communication, teamwork, and leadership skills (Zyblewski et al. 2019).

Understand Your Learner

Medical educators will typically be older than the learners they are teaching, and in many instances will be of an entirely different generation. Understanding the differences between learners of different generations is essential to establish a conducive learning environment and to ensure the successful transfer of knowledge. Medical trainees in the 2020s will typically be members of Generation Y (born between approximately 1981 and 1995) or Generation Z (born between approximately 1996 and 2012). Both of these cohorts have grown up with the Internet permitting immediate access to information at their fingertips. They are facile with technology and value creativity, teamwork, and interactive discussions over sitting in a classroom listening to a lecturer speaking at them (Rogers 2020).

Understanding the different learning styles of their student will be important for medical educators to develop effective curricula. Seasoned clinicians have a lot to teach. Matching teaching methods to the learners will optimize the chances of a successful medical education.

Use Technology to Your Advantage

The Internet has opened up the world to anyone with a smartphone or tablet. Even in low-income countries without a teaching hospital, the Internet allows learners to access a vast world of educational opportunities online—e.g., webinars, podcasts, telemedicine, even YouTube videos. Furthermore, the coronavirus disease-2019 (COVID-19) pandemic forced conferences to go virtual, which many appear to be continuing even as the world opens back up. While virtual learning is not able to fully replace hands-on training, they have created many new creative opportunities for medical education.

Many resources exist online with educational material regarding congenital heart disease.

- Heart University is a free website run by Cincinnati Children's Hospital Medical Center that offers material for both pediatric and adult CHD (www.heartuniversity.org).
- Open Pediatrics (www.openpediatrics.org) run by Boston Children's Hospital contains material for pediatrics in general and pediatric cardiology in particular.
- Pediatric Echocardiography (pedsecho.org) is a free site for pediatric echocardiography with learning modules for various lesions and includes a library of CHD images.

- The Association for European Paediatric and Congenital Cardiology website (www.aepc.org) includes information on European guidelines and recommendations.

Medical Simulation

Medical simulation can be a powerful option for medical education and a most cost-effective and potent option for institutions building up case volumes. Experiencing high-acuity events (e.g., cardiac arrest) in a simulated environment permits the learners to practice technical skills and decision-making without risk to a real patient. More importantly, well-designed and managed simulation courses can teach the arguably more important non-technical skills of communication, leadership, followership, and team cooperation. Medical simulation is versatile and can be employed with varying levels of cost (Park 2011; Chang 2013; Yunoki and Sakai 2018; Dabbagh et al. 2020). Simulation training can be executed in dedicated simulation teaching centers or at the bedside for in situ scenarios. Simulation can be used to teach complex decision-making in a plot-based scenario (e.g., management of pulmonary hypertensive crisis), or a specific task (e.g., chest tube for tension pneumothorax). Other learning objectives that simulation is well suited for are for teaching communication skills (e.g., disclosing bad news to a family), or team dynamics and leadership (e.g., training a code team). In situ simulation may be especially useful to orient new team members or to measure the readiness of a new ICU.

Conclusion

> It takes a village to raise a child. (African proverb)

The world has changed significantly in the last eight decades since the first congenital heart operation. A century ago, the lifespan of a baby born with congenital heart disease might be measured in minutes to hours. With modern technology and advances in the understanding of CHD, not only are children surviving, but also they are thriving. Success with children with CHD has given rise to greater numbers of adults with CHD. The supply of physicians in specialties caring for both populations has not kept up with the demand worldwide. Greater efforts are needed to improve the medical education of physicians and hospital staff to care for children and adults with congenital heart disease.

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