Jerrold Lerman
Editor

Neonatal Anesthesia

Second Edition

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I wish to thank my wife, Robin, and my children and grandchildren for their endless support and patience in undertaking this project.

I also wish to thank Drs. Robert E. Creighton and David J. Steward for their guidance and mentorship in shaping my academic career as a pediatric anesthesiologist.

Finally, not a day goes by that I do not reflect on the two anesthesiologists whose teaching, advice, influence, and mentoring set a trajectory for my academic career in pediatric anesthesia that would not have been possible otherwise: Drs. George Gregory and E.I. Eger II.

Thank you all.

Jerrold Lerman, MD, FRCPC, FANZCA

Foreword

The anesthesiologist … who has to spend more than a half hour in putting an infant to sleep because of unavoidable difficulties, and who during this time makes no excuses for his slowness and resorts to no drastic expedients to impress the onlookers or to console the impatient surgeon, is a gift beyond price to the welfare of children who are entrusted to his care in the operating room.—Willis J. Potts, *The Surgeon and the Child*, 1959

Those of us who have been privileged to practice neonatal anesthesia have indeed enjoyed a special relationship with our surgeons. We have also had to meet the challenges of working in one of the most demanding of anesthesia subspecialties. The technical aspects of our practice require a level of precision and attention to detail unparalleled in other areas of anesthesia practice. Successful perioperative management of the neonate requires obsessive monitoring and the potential for rapid and appropriate therapeutic responses based on a comprehensive knowledge of neonatal physiology and pharmacology. The neonatal anesthesiologist assumes a daunting responsibility, their patients are at a critical stage of development, and neonates are in the prelude to a potential lifetime of achievements.

Neonates have been given anesthetics since 1847, but the real history of neonatal anesthesia did not begin until halfway through the twentieth century. I started my training in pediatric anesthesia in 1967 at a world-renowned Canadian children's hospital. One day, I was assigned to assist with the anesthesia for a neonate with a pre-ductal coarctation of the aorta. I was told that the way to manage this patient was to give a large dose of d-tubocurarine (a paralytic drug) and ventilate the lungs with oxygen. My monitors included an esophageal stethoscope, an electrocardioscope, an oscillometer, and a rectal temperature probe. What a long way we have come in more than 50 years!

What you are about to read is the second edition of Neonatal Anesthesia. It is most appropriate that a comprehensive book devoted to neonatal anesthesia should be revised at this time. There has been a progressive and steady accumulation of knowledge related to the subject over the past few decades. Well-designed studies have been published, which now permit an evidence-based approach to anesthetizing the neonate. This, along with simultaneous widespread advances in medical technology, has provided clinicians with new and efficient means to improve all aspects of the neonate's care. All of this has culminated in a rapid evolution in the management strategies available for the neonate. The neonatal anesthesiologist can now very safely apply a full range of modalities to optimize the perioperative cardiorespiratory and overall physiological status, prevent pain, and contribute very significantly to the success of the surgery.

This second edition includes four new chapters that cover fetal surgery and the EXIT procedure, extracorporeal membrane oxygenation (ECMO), neonatal resuscitation, and the very important and somewhat controversial subject, "Do Anesthetics Harm Neonates." The chapter entitled "Metabolic Care" has been extensively revised to reflect the new insights and expanded evidence on this subject, and to recognize the importance of these advances in designing the perioperative prescription for the neonate. All of the remaining chapters have been revised and updated to incorporate the latest developments in their fields.

Dr. Lerman has a very extensive personal experience as a clinical neonatal anesthesiologist, gained in the very busy neonatal surgical service at the Hospital for Sick Children, Toronto, and subsequently at the Oishei Children's Hospital in Buffalo, NY. As an investigator, he has contributed significantly to our knowledge. He has recruited an outstanding international team of well-known contributors, each an expert in his or her field, that include neonatologists, intensivists, and pediatric surgeons in addition to pediatric anesthesiologists, to compile this sourcebook for the practitioner.

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June 2022

David J. Steward

Acknowledgments

We thank the authors for their excellent contributions to the first edition of Neonatal Anesthesia.

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The History of Neonatal Anesthesia

1

David J. Steward

Prelude

Operations in neonates were sometimes undertaken in the years before the introduction of anesthesia. Those procedures most frequently documented were imperforate anus and harelip (cleft lip). Harelip repair was quite often successful, whereas imperforate anus procedures were often followed by death. Many surgeons were reluctant to operate on neonates and there was controversy regarding the propriety of these procedures [1]. In 1833, Wardrop observed that "Infants are sometimes destroyed by the loss of even a small quantity of blood," although he also reported the successful repair of a double harelip in an 8-day-old child and preferred to operate on the infant at an early age [2]. At the same time, he was concerned that the emotional effects of the mother or nurse (i.e., "wet nurse") observing the infant's distress during the operation might alter the composition of her breast milk. This concern was then used to explain the cause of convulsions and death, which sometimes ensued. Indeed, he suggested that "neither the mother nor the hired nurse should be agitated by the screams of the child or that if they be at all alarmed by them the child should not be allowed to suckle until all effects of such agitation have ceased."

Considering our present knowledge of the adverse physiological effects of unmodified pain on the neonate, it is not surprising that surgery without anesthesia was often unsuccessful. It is somewhat surprising that though poppy extract (opium) had long been administered to infants who were crying with the discomforts of teething [3], there are no reports of its use to ease the pain of surgery.

The introduction of general anesthesia had the potential to render operations in neonates much more acceptable to all those who were involved (not least the patient!); however, it was to be a long time before such anesthesia was universally and effectively administered.

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Early Times

Diethyl ether was administered during operations by Crawford Long in 1842, but it was the demonstration by William G. Morton in 1846 at the Massachusetts General Hospital in Boston, Massachusetts, that led to the widespread introduction of general anesthesia. However, the benefits of anesthesia during surgery were not immediately or universally applied. "They don't feel it like we do" was a saying held to be true by physicians and surgeons long after 1846 [4]. In 1847, one-third of the surgical operations on adults at the Massachusetts General Hospital, the site of Morton's demonstrations, were performed without anesthesia [4]. Anesthesia was selectively applied to those who it was judged felt pain more severely, i.e., white, wealthy, and especially female patients. Infants, in particular, were considered incapable of perceiving pain; indeed Dr. Abel Pierson stated that "infants could sleep insensibly even while undergoing surgery" [4]. Henry J. Bigelow considered that like the lower animals, the very young lacked the mental capacity to suffer pain [5]. Indeed, in the case of the neonate, misunderstanding of their perception of pain persisted well into the twentieth century.[1]

During the second half of the nineteenth century and the early part of the twentieth century, the decision to administer anesthesia to a neonate to relieve the pain of surgery was inconsistent. This is perhaps not surprising given the primitive methods that were available to administer anesthesia, the rarity of neonatal surgery, and the fact that small infants could be quite easily restrained during an operation (in addition to the thought that they do not feel pain anyway!).

[1] As recently as 1976, a technique of "anesthesia" for ductus arteriosus ligation in preterm infants, which was totally devoid of anesthetic or analgesic agents, was reported from a large American University Hospital in a widely respected British journal. The authors stated "No premedication was given. Just before the procedure, if necessary, a paralysing dose of suxamethonium 1 mg/kg body wt. was given. No other anaesthetic agent was used…We have avoided the use of anesthetic or analgesic agents which in our opinion are unnecessary" [6].

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Reports of operations on "impervious rectum" [7], strangulated inguinal hernia, and even meningomyelocele [8] without anesthesia can be found in medical journals of this era.

However, reports from this same time period can also be found describing anesthesia that was administered to infants in the first month of life. John Snow preferred chloroform and wrote in 1855 "Chloroform may be given with propriety to patients of all ages. I have exhibited it to several infants aged from ten days to three weeks" [9]. He went on to say that "Chloroform acts very favourably on infants and children. There has, I believe, been no death from chloroform under the age of fifteen years." The most commonly described indication for elective surgery in neonates during these years was for correction of "harelip," an operation that was frequently performed "at the earliest period of life."[2] On Saturday, July 4, 1857, an entry in the case books of John Snow [10] reads "Administered Chloroform at Kings College Hospital to an infant, 8 days old, previous to Mr. Fergusson operating for hare-lip. The face piece was too large and the chloroform took very little effect." Chloroform was administered on this occasion using Snow's inhaler with a small facepiece; the latter, however, was still too large for a neonate. According to Snow, the use of the inhaler permitted "a more gradual introduction of the agent than when administered on a sponge or handkerchief" [9].

The alternative method was to administer chloroform to the infant using a sponge. "Mr. Greenhalgh preferred a sponge to every other kind of apparatus. He had employed the chloroform in a great number of cases, and with success: one of the cases was an infant, three weeks old, for an operation for hare-lip" [11].

During the second half of the nineteenth century, neonatal surgery was limited to superficial lesions. Abdominal surgery was largely confined to the emergency management of incarcerated inguinal hernia. Imperforate anus of the low type was relieved by incision, often without anesthesia. There were also reports of successful operations on neonates under chloroform anesthesia for high imperforate anus. Thoracic surgery was certainly not attempted. However, during these years, great progress was achieved in basic surgical techniques and the prevention of infection. The concepts of antisepsis and asepsis were recognized and applied. Many of the congenital lesions that would much later become the field of the neonatal surgeon were being recognized—though only as curiosities [12].

It is during this time that the first books on pediatric surgery were being published and special hospitals for children were being established. The Hospital for Sick Children at Great Ormond Street in London (GOS) in England opened in 1852; the Hospital for Sick Children, in Toronto, Canada opened in 1875; and Boston Children's Hospital, in the USA, which was modeled after GOS, opened in 1882 [12]. Other European and North American cities established children's hospitals at about this time. "Pediatric surgery" in these early years involved mainly orthopedic procedures, neonatal surgery was rarely performed, but the children's hospitals would serve as a site and a catalyst for the subsequent expansion of infant surgery.

In the late nineteenth century, progress was being made in the care of the sick neonate and preterm infant. It was recognized that the survival of small preterm infants was improved if they could be kept warm. A warm-air heated incubator was developed by a French obstetrician, Stephane Tarnier, and installed at the Paris Maternity Hospital. This was based on a device for raising poultry, which Tarnier had seen at the zoological garden [13]. The design was improved by Pierre Budin, and his incubators were shown at the Berlin World Exhibition of 1896 by his associate Martin Couney, infants being provided by Dr. Czerny, who was the Professor of Pediatrics in the city. Couney later exhibited his incubators in London and at the Pan-American Exposition in Buffalo, New York, in 1901. He also opened an exhibit at the Coney Island fairground in New York City, which ran until 1943. Infants in incubators were also displayed at various other public exhibitions and fairgrounds. The public was invited to pay 25 cents to view these infants in incubators, an unlikely start for the specialty of neonatology. Once having been used in an exhibit, many incubators were later sold to hospitals.

The Twentieth Century

In 1905, ethyl chloride was being used for brief procedures in infants as young as 5 days of age. It was administered using an inhaler [12, 14, 15]:

> A celluloid face-piece is generally preferable since it not only permits the anaesthetist to observe the patient more readily but also resists the action of the vapour better than rubber. For infants of a few days or a few weeks old I commence by spraying three cubic centimetres into the inhaler; for those of six months and upwards I give five cubic centimetres at once. The mask is then approached to the face but not pressed against it so that the baby has several breaths of air and vapour mixed; it is then more closely applied so as to exclude all air except that which is already in the bag, and in a few seconds the child becomes unconscious. When one is sure that the anaesthesia is deep and the surgeon has made his incision or begun the operation the mask should be removed from the face and a few breaths of air should be given. If it is desired to continue the period of narcosis for some time the mask should not be kept off for long but only raised occasionally for air. If the respiration indicates the lightening of the narcosis a few more cubic centimetres may be added to the bag; on these lines the anaesthesia may be indefinitely prolonged.

[2] Repair of cleft lip ("harelip") today conjures up thoughts of a delicate procedure with carefully planned and positioned skin flaps sutured using many fine sutures in a procedure lasting an hour or more. In the 1850s, the repair would require 3–5 sutures and be completed within 3–5 min, at most.

Abdominal surgery for infants became established around the turn of the twentieth century with the introduction of surgical procedures for the relief of pyloric stenosis. Originally managed by gastroenterostomy, the lesion was later corrected by pyloroplasty [16] and finally by Ramstedt's extramucosal pyloromyotomy [17]. Though most patients were older, some neonates were operated upon for pyloric stenosis. Chloroform was the preferred anesthetic and the need for adequate and constant levels of anesthesia was recognized. Reporting success in their cases of pyloroplasty in the Lancet in 1902, Cautley and Dent stated: "Unless the patient is deeply under the influence of chloroform (which certainly appears to be the best anaesthetic) there is risk of protrusion of the intestine and rapidity of operating becomes a matter of great difficulty. On the other hand, in abdominal operations on very young children deep anaesthesia, unless most carefully induced and maintained, may lead to very sudden and alarming symptoms. Any interruption to the operative procedure while in progress would be a very serious matter, for if the patient is not deeply anaesthetised there is every likelihood of his recovering sufficiently to cry or to struggle. If any such event happens the intestines are likely to protrude at once with the most astonishing suddenness and force. In a case recorded by Stern; both of these troubles seem to have occurred. The child's breathing stopped just after the operation had begun; the anaesthetic was so badly borne that it had to be discontinued while the operation was completed; and the result was that the intestine protruded extensively, thus prolonging the operation and enormously increasing its severity" [16]. There followed a much-deserved tribute to the skill of their own anesthetists: "The success of our cases was largely due to the extreme care and skill with which the anaesthetic was administered, in the first case by Dr. H. Menzies, and in the second by Dr. G. P. Shuter. The surgeon is too often inclined to absorb all the credit of a successful operation, when a great part of it is really due to the anaesthetist" [16]. Anesthesia for infants was already recognized as requiring special attention to detail.

Monitoring during these early years depended on observation of the patient's color, the pattern of ventilation, and in older patients perhaps a finger on the pulse! Much skill must have been needed to maintain an airway without instrumentation, ensure a constant level of anesthesia, and avoid cardiorespiratory depression. It is not at all surprising that the mortality rate for infants was very high. However, some amazing successes were reported with what must have been very challenging clinical cases. One such was the resection of an extremely large teratoma from the neck of a child 3 weeks old [18]. Anesthesia was induced and maintained with chloroform on a sponge. "The element of time was necessarily a most important point in the operation and it was hoped that as the cyst wall was well defined it might be possible to shell out the tumour throughout the greater part of its extent. This fortunately proved to be the case and the whole operation lasted only 12 min, notwithstanding the fact that the work had to be stopped every few seconds to allow the infant to breathe. In order to diminish the duration of the operation and the amount of shock a continuous catgut suture was used and no attempt was made to remove the superfluous skin" [18].

These then were the early days of neonatal surgery. The treatment of major congenital anomalies would have to await further progress in the perioperative and anesthesia management of the infant. One major step forward was the introduction of endotracheal anesthesia and the associated potential for controlling ventilation.

Endotracheal Intubation of Neonates

MacEwen introduced the concept of passing tubes through the adult glottis into the trachea as an alternative to tracheotomy in 1880 [19]. Elsberg passed intratracheal catheters and used these to insufflate anesthetic gases describing his technique in 1909 [20]. When using an intratracheal insufflation technique, a small catheter was utilized to leave an adequate route for expired gases. Indeed, common practice was to pass a second catheter through the glottis to provide a reliable route for expiration. This prompted C Langton Hewer, who a year later was to write the first British text on pediatric anesthesia, to state in 1924: "Endo-tracheal anaesthesia is contra-indicated in the following class of case:—Babies below the age of one year. The lumen of the glottis is so small in babies that it is practically impossible to obtain a catheter of such size as will permit sufficient vapour to pass and yet leave an adequate return airway" [21]. However, also in 1924, Ivan Magill did describe an expiratory attachment for an intratracheal catheter, which was available in five sizes—the smallest of which would attach to a 9-French catheter (i.e., a 3-mm external diameter catheter) [22]. The expiratory attachment was essentially a tapered metal tube, which could be sited at the level of the glottis and connected to a second catheter. He later reported that he had used this tube attachment in children under 2 years.

In 1928, Magill was routinely using endotracheal tubes of sufficient caliber to permit *to-and-fro* ventilation, a method he preferred in small children and which he had first used in adults in 1920 [23]. Magill tubes were manufactured of red rubber and the smallest size was 00 which had an external diameter of 4 mm, similar to that of today's 3.5-mm ID plastic tube, though the internal diameter of the Magill 00 tube was only 3 mm.

In 1939, Gillespie described methods for routine tracheal intubation of infants [24]. He stressed that though the advantages of intubation were now universally accepted, the intubation itself was more difficult in infants and, in inexperienced

hands, might endanger the patient. To facilitate intubation, he favored a nitrous oxide/oxygen mixture with ether anesthetic and added 5% of carbon dioxide to induce hyperpnea and speed induction. When respiration was regular and automatic, the mandible relaxed, and no trace of glottic spasm evident, intubation could be attempted. (There were, of course, no relaxant drugs available at this time.) He had developed a modification of the smallest-size Chevalier Jackson laryngoscope, which was marketed under the name "Shadwell" laryngoscope (Fig. 1.1). It was designed to be held with the fingers rather than in the palm of the hand "to discourage the use of force" [24].

Gillespie noted that the epiglottis in the neonate was proportionally longer than in the adult and that, with each breath, the larynx tended to move anteriorly and out of the field of vision; deepening the anesthetic to prevent this movement tended to induce signs of impending cardiorespiratory failure. He stressed the need for gentleness and warned that any use of force might cause complications varying from a croupy cough to acute edema of the larynx. In his own reported series of 70 infants under the age of 2 years, he had remarkably few complications, especially in view of his statement that the largest possible tube should be passed. He was concerned to not narrow the airway, as all his patients were breathing spontaneously. However, he did stress the need to attempt to pass the tube "gently" [24].

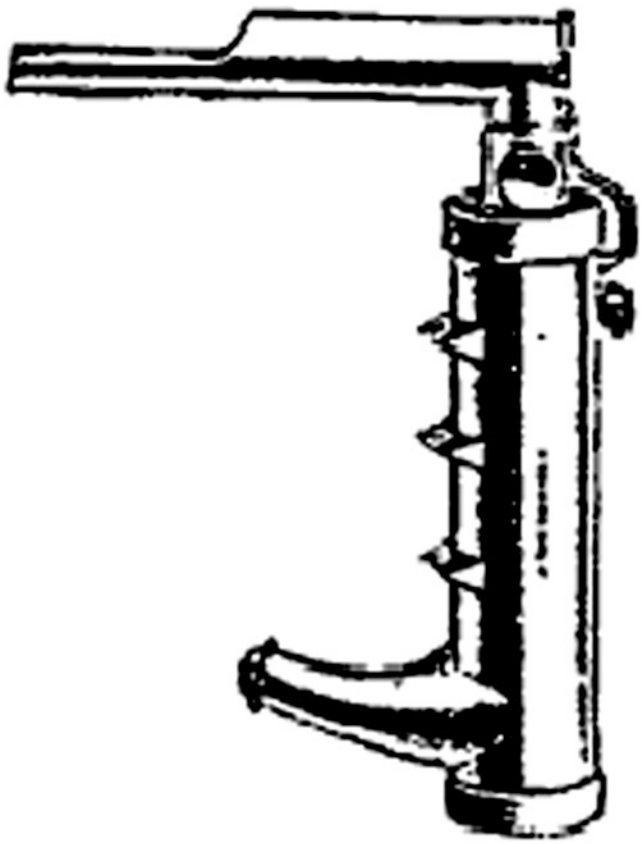

Fig. 1.1 The Shadwell laryngoscope

The use of endotracheal intubation in infants was not without problems, however, and cases of postoperative laryngeal edema and, more rarely, subglottic stenosis were reported. The need to use a tube, which passed easily through the glottis and subglottic space and allowed a slight leak on pressurization of the anesthesia circuit, was, in time, recognized by anesthesiologists. A classic paper by Eckenhoff [25] in 1951 described the anatomy and dimensions of the infant larynx and stressed the need to avoid injury to the mucosa in the region of the cricoid ring. The problems that sometimes followed intubation and the fear that these might adversely affect outcomes led many surgeons, particularly in the USA, to oppose this practice for their patients. Anesthesia providers were directed to manage neonates for complex repairs, e.g., tracheoesophageal fistula or coarctation of the aorta, using mask anesthesia. However, the pioneers of pediatric anesthesia persisted, perfected safer methods, and thus facilitated acceptance of the need for endotracheal intubation, essential if progress in neonatal surgery was to continue.

Red rubber tubes were largely abandoned in favor of plastic tubes in the 1950s. However, early plastic tubes were also not without problems. Irritant chemical substances (organotins) within the plastic material were found to be capable of stimulating local tissue reactions that could lead to fibrosis [26]. The establishment of routines for implantation testing of plastic material led to improvements in endotracheal tube composition and manufacture and a subsequent decrease in complications.

In 1945, Cole described a new endotracheal tube for infants. This tube had a wider proximal portion and a narrower distal segment to pass through the glottis, the rationale being that the wider portion would decrease the resistance to airflow. In addition, it was claimed that the shoulder of the tube would decrease the likelihood of the tube passing too far and entering a bronchus. In fact, the resistance of the Cole tube was found to be greater than that of a similar internal diameter parallel-sided tube [27]. This was attributed to turbulent flow within the Cole tube. More seriously, the shoulder on the tube was shown to cause laryngeal damage if advanced into the glottis [28]. The Cole tube was generally abandoned for use during anesthesia but remained in use for neonatal resuscitation in some centers, the claim being that it was easier for the less expert practitioner to insert.

The concept of prolonged endotracheal intubation as an alternative to tracheostomy was presented by Bernard Brandstater at the First European Congress of Anesthesiology in 1962 [29]. He reported his experience with seven patients ranging in age from the neonate to 4 years. Until that time, it had been customary to perform a tracheostomy if infants required ventilator assistance [30]. The tracheostomy tubes

in general use were uncuffed and the variable leak that occurred via the glottis made a constant level of ventilation difficult to attain—especially in patients with reduced pulmonary compliance. Fortunately, the ventilators in common use in North America at this time were pressure cycled (the "Bird" Mark VIII) and this reduced the problem to some extent. In mid-1960s, the use of intermittent positive pressure ventilation (IPPV) in the therapy of newborn respiratory distress syndrome was becoming established as was the need to treat respiratory insufficiency in the postoperative cardiac patient [31]. In 1965 Reid and Tunstall reported a case of respiratory distress syndrome in a 1800-g preterm infant successfully treated by IPPV via a 2.5-mm ID nasotracheal tube [32]. In the same year, McDonald and Stocks from the Royal Children's Hospital in Melbourne, Australia, reported a larger series of infants treated with prolonged nasotracheal intubation [33]. They described the complications, including post-intubation subglottic stenosis, and offered suggestions to minimize the incidence of this serious outcome. By the end of the 1960s, prolonged endotracheal intubation had superseded tracheostomy as the management of choice for infants requiring ventilatory assistance.

During the 1960s and 1970s, it was a very common, almost standard, practice to intubate the trachea while the infant was awake, before induction of anesthesia. This, it was claimed, minimized the danger of regurgitation and aspiration and facilitated the rapid induction of anesthesia [34]. In addition, if attempts at intubation failed, there was little danger as the infant would usually maintain the airway and continue ventilation. Awake intubation of the neonate continued to be widely practiced until toward the end of the twentieth century when concerns about the physiological stress that might be imposed on the infant prompted further consideration [35]. In addition, it was demonstrated that intubation is much more likely to be successful with fewer attempts and less elapsed time if performed in the anesthetized infant [36].

Having intubated the airway in the neonate, the scene was set to control ventilation during anesthesia. This would facilitate procedures to correct intrathoracic congenital defects. In addition, it would allow the administration of neuromuscular blocking drugs to provide optimal conditions for abdominal surgery and reduce the need for high concentrations of inhaled anesthetics.

Neuromuscular Blocking Drugs

d-Tubocurarine was introduced into anesthesia practice in the 1940s and succinylcholine became available in the 1950s. Both drugs were used in neonates soon after their introduction, but initially, there was a lack of universal enthusiasm for using relaxant drugs in the neonate. In Europe, a pioneering neonatal anesthetist, Dr. Jackson Rees, wrote in 1950 "In the newborn, as has already been shown, control of the respiration is easily obtained at light levels of anaesthesia without the use of relaxants: muscle relaxation does not appear to be of major importance in the production of good operating conditions, and the usual untoward effects of endotracheal-tube induction are not seen.(sic) On these grounds it can be said that the use of relaxant drugs in anaesthesia is contraindicated in the newborn patient, and I have abandoned these drugs in such cases" [34].

In the USA, the study of Beecher and Todd published in 1954 [38] demonstrated an increased mortality associated with the use of relaxant drugs—especially in those in the early years of life. Postoperative respiratory difficulties were reported in infants given relaxants [39]. In 1955, Stead reported that the neonate was sensitive to the effects of non-depolarizing neuromuscular blocking drugs but was resistant to the effect of the depolarizing drug succinylcholine [40]. This further supported the impression that residual curarization was a problem in infants. However, Rackow and Salanitre in New York reported their experience with relaxant drugs [41] and suggested that postoperative respiratory depression was seen only as a result of drug overdose or with hypothermia; the latter was not uncommon at that time in the smaller infants. Warming from hypothermia had been demonstrated to potentiate any residual block [42]—hence, the infant placed in a heated isolette to rewarm after surgery was at risk! This observation encouraged efforts to maintain normothermia during neonatal surgery (see below).

In the 1960s, the use of neuromuscular blocking drugs in the neonate was widely accepted, and the use of heating blankets and overhead warmers to maintain normothermia became routine. Rees wrote "Following intubation the child may be saturated with nitrous oxide as rapidly as possible by intermittent positive pressure ventilation, and the relaxant drug may then be administered. In this way perfect operating conditions are obtainable, and the more potent and, therefore more toxic agents are eliminated from the anesthetic technique" [37]. This was the "Liverpool technique," which was widely used in Britain and elsewhere. For brief procedures, it was not uncommon to use repeated injections of succinylcholine as a relaxant.

The question of the sensitivity of the neonate to d-tubocurarine (dTc) was finally resolved by Fisher in 1982 [43]. The neonatal neuromuscular junction is indeed sensitive to the effects of dTc, but this is largely compensated by the increased volume of distribution of the drug in this age group [43].

Anesthesia Circuits and Controlled Ventilation

The T-piece system was considered by many to be the anesthesia circuit of choice for the neonate. It is lightweight and simple and has low dead space and low resistance, and ventilation could be controlled simply by intermittently occluding the expiratory limb with the finger. Jackson Rees in Liverpool improved on this system by adding an open-ended bag to the end of the expiratory limb [34]. A vulcanite tap was inserted into the open end of the bag and adjusted to maintain the bag inflated but to allow escape of expired and excess gases. Manual controlled ventilation was readily applied with this system. However, a fresh gas flow of 2–2.5 times the minute ventilation was required to prevent rebreathing of expired gases. This was wasteful of anesthetic gases, which were cheap in those days, and potentially caused significant atmospheric pollution (not appreciated to be a problem until the 1970s). A modification to prevent rebreathing with lower fresh gas flows was to use a small-sized Waters soda lime canister on the expiratory limb for CO_2 absorption, but this was generally considered less easy to apply to the small infant. Indeed, Leigh and Belton writing in 1950 stated "Use of absorption technic in the first few months of life is impracticable and affords no distinct benefits to patient, surgeon and anesthesiologist" [44].

The pattern of ventilation chosen by the Liverpool group for infants is interesting. Dr. Jackson Rees always encouraged the use of rapid shallow ventilation for the neonate. He admitted that this often led to hyperventilation and hypocapnia but did not consider this to be a significant problem [37]. In later years, he would add small concentrations of carbon dioxide to the inspired gases when indicated to prevent hypocapnia (Rees GJ, personal communication). The pattern of ventilation used, however, did tend to limit the duration of expiration and maintain a constant positive pressure—both of which acted to reverse the reduction in lung volumes that occurs during anesthesia and muscle paralysis and thus improve gas exchange. Dr. Rees was quite gratified to read much later of the clinical studies that defined adverse changes in pulmonary function which accompanied infant anesthesia, changes which his technique had tended to moderate.

As neonatal surgery became more complex and longer procedures were performed, the need to provide for mechanical ventilation during surgery was apparent. Fortunately, by this time, progress in ventilator design made this possible. Quite simply, the Bird Mark VIII ventilator or the Ohio Ventimeter Ventilator could be adjusted so that they would periodically serve to occlude the expired limb of a T-piece system.

As an alternative to the T-piece system, which required a fresh gas flow 2–3 times the minute ventilation to prevent rebreathing, some anesthesiologists preferred to use non-rebreathing valves. These required only a gas flow equal to the minute ventilation. Ronald Stephen and Harry Slater described their non-rebreathing valve in 1948. It incorporated two rubber valves and was described as having very low resistance to breathing and negligible dead space. Controlled ventilation could be delivered by compressing the exhalation valve with a finger while compressing the reservoir bag, and the authors claimed to have used this method in infants of 3 weeks for up to 90 min [45]. In 1948, Digby Leigh independently described a valve of very similar design, which could be used in infants [46]. George Lewis modified the Leigh valve to permit controlled ventilation without the need to digitally compress the exhalation valve. The Lewis/Leigh valve incorporated a flap that would close the exhalation port if the reservoir bag were compressed [47].

A problem with the T-piece system and with non-rebreathing valves was that they delivered very dry gases to the airway. In the USA, this concern led to the development of circle systems modified for the neonate. The Bloomquist infant circle was marketed by the Foregger company and incorporated a soda lime canister. However, a laboratory study of the humidity output of this circuit concluded that it offered no advantage over a humidified T-piece system and was more cumbersome to use [48]. The Columbia Valve was developed to allow a modified adult circuit to be used for infants; the valve had low resistance and a very low dead space of 0.5 mL [49]. This valve was used in a circuit in which the fresh gases were passed through the soda lime canister together with the expired gases in an effort to maximize the level of humification (Rackow H, personal communication). The T-piece and its variants were almost always used for the neonate in Britain and Canada; non-rebreathing valves and various circle absorber systems were more commonly used in the USA.

In later years, pediatric anesthesiologists adapted various neonatal ventilators for operating room use. Progressive improvements in anesthesia machine design eventually allowed small infants to be successfully managed simply by changing to a smaller-diameter set of circuit tubing.

Monitoring

As has been stated previously, monitoring in the early days consisted of watching the chest movements, examining the color, and perhaps feeling the pulse. Indeed, this situation persisted well into the twentieth century. Writing on anesthesia for neonatal chest surgery in 1965, Bell stated "*A guide to the general clinical condition I find useful is this:*

> *baby pink and pulses palpable-condition good;*
> *baby pale, pulses palpable or baby pink, pulses not palpable-condition satisfactory, but check ventilation and blood balance;*
> *baby pale, pulses not palpable—condition serious.*

I do not think that cardiac stethoscopes (the heart action can be seen in thoracic operations), sphygmomanometers, pulse monitors or E.C.G. tracings contribute enough additional information about a baby's condition to merit their use; they may be distracting" [50].

I cannot say that this was the general attitude to monitoring in those years, but it is a recorded opinion.

Accounts of neonatal anesthesia prior to 1960 make little or no mention of monitoring [34, 37, 39]. In fact, the technology to satisfactorily monitor blood pressure in the neonate was not generally available until the late 1950s. Palpation or auscultation distal to a blood pressure cuff was noted to be very difficult in small infants. Oscillometry had been used but was not uniformly reliable. Hence, it was not common practice to monitor the blood pressure even in larger infants. Anesthesia records from this era commonly displayed only a heart rate. In an article on anesthesia for major surgery in 1950, CR Stephen displayed an anesthesia record for pyloromyotomy on which the only vital signs recorded were the heart rate and respiratory rate [51].

The optimal width of the blood pressure cuff (one inch) that was required for accurate measurement in the neonate was determined in 1939 by direct comparison with an intra-arterial needle [52]. However, as noted above, it was uncommonly used in anesthesia practice. Detection of pulsation distal to the cuff most often depended upon oscillometry. To detect the very small deflection of the oscillometer needle was frequently highly dependent upon "the eye of faith." This could be very worrying during thoracic surgery or indeed any other major procedure; this I remember well.

In 1969, the use of the Doppler flow meter to monitor flow in the radial artery distal to a blood pressure cuff and reliably measure intraoperative blood pressure in infants was reported [53]. The battery-operated "Parks Doppler Flowmeter" became widely available and took much of the worry out of neonatal anesthesia. It could be used to measure blood pressure and also served as a continuous audible monitor of the pulse volume, serving as an early warning of adverse changes.

Direct intravascular measurement of the arterial pressure was initially measured from the umbilical artery; however, this resulted in a relatively high incidence of serious complications (e.g., bowel infarction) and was only applicable in the immediate neonatal period. Percutaneous cannulation of the radial artery in neonates was described in 1975 as a safer alternative [54, 55]. The use of the temporal artery for monitoring was also suggested [56] but was later generally abandoned when it became known that cerebral embolism was associated with this technique [57]. Femoral artery lines were also used on occasion but, in the neonatal age group, the incidence of ischemic complications exceeded that with radial lines [58].

In 1950, the monitoring of the oxygen saturation of blood during anesthesia was described by a group from Montreal [59]. They used an earpiece, which had been developed during World War II for the purpose of studying pilots flying at various altitudes. The equipment they used was delicate, however, and required a dedicated technician to operate it. Continuous monitoring of transcutaneous oxygen tension ($TcpO_2$) in neonates was described in 1972 [60], but this was not introduced as a routine into the neonatal nursery for several years. Though $TcpO_2$ was capable of indicating trends, individual readings lacked precise accuracy especially with decreased skin blood flow [61]. Electrodes required frequent attention and had to be moved periodically to prevent burns. During anesthesia, inhaled agents were found to further interfere with the performance of the electrode and decreased its accuracy, though not to a significant degree [62].

Pulse oximetry became available for clinical use in 1983 [63] and was rapidly adopted as a routine monitor during the surgery and acute care of neonates; it was far easier to apply than the TcpO2 electrode and did not require repositioning periodically. It was now possible to continuously display the level of oxygenation throughout the perioperative period and immediately respond to any adverse changes. It was also quite possible to apply two probes: one in the preductal area and one in the postductal area. The question now arose as to the safe level of preductal oxygen saturation to maintain in the preterm infant at risk for retinopathy of prematurity (ROP). Surveys performed in recent years indicate that many units aim to maintain SpO_2 in the 85–93% range [64] and that this does indeed decrease the incidence of serious ROP changes [65].

Monitoring of end-tidal carbon dioxide as a routine procedure in anesthesia care became commonplace during the 1980s. When applied to the neonate, it became apparent that both methods for CO_2 analysis, mainstream and sidestream, are problematic [66]. The increase in dead space with mainstream analysis may lead to rebreathing in small infants. During sidestream analysis, the site of sampling, the sampling flow rate, and length of the sampling tube proved to be critical factors in obtaining accurate measurements of end-tidal CO_2.

Intraoperative Temperature Control

As more prolonged surgery was being performed in neonates, the problem of intraoperative hypothermia became recognized [67] and identified as a cause of increased morbidity and mortality [41, 68–70]. Two of five postoperative deaths in a series of 12 neonates were attributed to hypothermia [68]. In another series of 67 infants, 12 patients died; seven of these were judged due to postoperative hypothermia

[70]. It was noted that the decrease in body temperature was directly related to the duration of surgery and that smaller infants suffered a greater decrease. The vulnerability of the small infant to heat loss as a result of the large body surface area to weight ratio was noted [71]. At this time in the 1950s, little was done to keep the neonate normothermic during surgery and indeed intraoperative hypothermia was considered by some to be beneficial.

An improved understanding of the adverse physiological effects of hypothermia came in the early 1960s. It also became recognized that it was much easier to keep the patient warm during surgery than to resort to rewarming postoperatively. The adverse effects of cooling on oxygen consumption [72], catecholamine levels [73], and acid/base status [74] were identified. Oxygen consumption in the neonate was shown to correlate most closely with the skin to environment temperature gradient, hence the significance of the "neutral thermal environment." With this new understanding, efforts were made to maintain normothermia intraoperatively. Hot water bottles alongside the infant were recommended, but unfortunately, this sometimes led to burns. Heating pads for the operating room table were described by Leigh and Belton in the second edition of their book on pediatric anesthesia published in 1960 [75]. Wrapping the limbs in cotton wadding and placing the infant on a warming blanket set at 40°C were advocated by RM Smith in his textbook in 1968. It was also found that heating blankets were more effective in maintaining normothermia in smaller infants—a beneficial effect of the large surface area to body mass ratio [76]. The addition of overhead radiant heaters during preparation for surgery and humidification of anesthetic gases provided for what was considered optimal patient management in the late 1960s and 1970s [77]. In the 1990s, forced air warmers became generally available and proved very effective in maintaining normothermia [78].

Neonatal Anesthesia: Some Landmark Procedures and Their Development

Repair of Esophageal Atresia and Tracheoesophageal Fistula

The first operation for esophageal atresia was performed in London, England, by Charles Steele in 1888 [79]. The diagnosis was made when the infant became livid and had difficulty breathing "after the first nourishment"; a sound could not be passed by mouth for further than 5 inches. Surgery was performed the next day after "the infant took chloroform well." The stomach was opened via an abdominal incision and an unsuccessful attempt was made to pass a gum elastic catheter retrograde up the esophagus, in the hope that a simple membrane could be perforated. The surgery was abandoned and the infant died 24 h later.[79] At autopsy, the upper and lower esophagus ended blindly one and one-half inches apart. There is no mention of an associated fistula.

The first successful ligation of a tracheoesophageal fistula (TEF) with anastomosis of the associated esophageal atresia was reported by Haight in 1943 [80]. Local analgesia was used for the first part of the operation; open ether was added during the esophageal anastomosis in order to obtain optimal surgical conditions. Spontaneous ventilation was maintained throughout. In Britain, Franklin described two successful repairs of TEF with esophageal anastomosis in 1947 [81]; both of these procedures were performed using infiltration of local anesthetic (1% procaine) to the chest wall incision line and no other anesthesia. During the operation "the infant was secured prone over a rubber hot water bottle" [81].

As has been previously stated, in early days, many surgeons opposed the use of endotracheal intubation for their patients. Swenson, a much respected pioneer pediatric surgeon, reported his experiences with TEF in 1943 and advocated the administration of cyclopropane via a tightly applied face mask [82]. Kennedy and Stoelting reported a series of 86 cases of TEF operated upon at Indiana University Hospital from 1940 until 1956 [83]. Before 1948, 17 cases were managed without intubation using a combination of local analgesia and open ether; the mortality rate was 88%; two patients died during surgery. After 1948, all 69 neonates underwent tracheal intubation, none died during surgery, and the overall mortality rate was 42%. Many factors were considered responsible for these improved results, but the role of endotracheal intubation and tracheobronchial toilet was considered to be very significant. General anesthesia methods reported by Zindler and Deming in 1953 [84] employed awake endotracheal intubation to administer cyclopropane via a non-rebreathing valve and controlled ventilation. They also stressed the need for frequent suctioning of the trachea.

Progressively improving results from the surgical and anesthesia management of TEF can be followed by examining the Toronto experience. A review of the results from 1959 to 1964 [85] shows an overall mortality rate of 36.5%, with a rate of 57.5% for the infants who were under 2500 g body weight. The predictors of mortality were prematurity, the presence of associated congenital malformations (especially cardiac), and extensive pulmonary disease (i.e., delayed diagnosis). A subsequent review [86] of the years 1964–1968 noted an overall mortality rate of 22%, and the mortality rate for those under 2500 g had decreased to 40%.

The problem of gastric distension due to gases passing through the fistula into the stomach was a concern for the anesthesiologist, especially as this has been reported to cause serious ventilatory embarrassment and even cardiac arrest [87]. Some preferred to maintain spontaneous (perhaps gently assisted) ventilation until the fistula was ligated. Other suggestions to prevent this complication included perform-

ing a preliminary gastrostomy under local analgesia [88]; this was also favored by some surgeons as part of a two-stage repair, especially in critically ill infants. Passing an endotracheal tube (without a side hole) into the bronchus and withdrawing it until bilateral ventilation could be heard and then positioning the tube with the bevel facing anteriorly were also suggested [89]. This would direct ventilation to the lungs and protect the fistula with the longer side of the bevel. (However, the fistula is occasionally at the level of the carina!) Some more complicated methods to position the tube and prevent gastric distension have also been described. If a gastrostomy was present, it was suggested that placing the gastrostomy tube under water in a beaker while advancing the endotracheal tube could indicate when the ETT was below the fistula [90], i.e., no more bubbles! The significance of leaks via the fistula increased as preterm infants with respiratory distress syndrome requiring greater airway pressures presented for surgery. Karl suggested that a balloon catheter should be inserted into the lower esophagus via the gastrostomy to control the leak [91]. Others suggested that a Fogarty or pulmonary artery catheter should be advanced via a bronchoscope directly into the fistula [92]. In many units, it became a routine to perform early ligation of the fistula in preterm infants, thus largely avoiding the problem.

Preoperative endoscopic examination of the fistula was introduced in the 1980s [93] and became routine in some centers [94]. It was suggested that an exact knowledge of the size and site of the fistula would improve results and in addition endoscopy permitted placement of balloon catheters to occlude the lumen. Others preferred to keep things simple and manage the airway without endoscopy [95].

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) was described in 1757 by a society of physicians in London following postmortem examination of an infant who died under 2 h of age in respiratory distress [96]. Early reports of operations for CDH are found in the medical literature of the 1930s [97] and 1940s [98], but it is significant that the neonates were all more than 20 h of age, and some patients were much older, i.e., they had adequate pulmonary function to survive the immediate neonatal period. In 1946, Robert Gross reported seven cases that came to surgery with ages ranging from 22 h to 7 years; he also recorded his preferred anesthesia technique [98]:

> *The choice of anesthetic agent and the method of its administration are important considerations, particularly in the cases of patients in whom cyanosis and respiratory embarrassment are pronounced. Ether can be employed, and indeed may be given with an open mask. It is preferable to use a closed system, so that a higher percentage of oxygen can be supplied to the patient and so that collapse of both lungs can be prevented in those rare cases in which there is a free communication between the two pleural cavities. In all cases of the present series, cyclopropane was used and was eminently satisfactory. It is clear, however, that this choice depended on my good fortune in having an anesthetist who is expert in handling babies and who has had enough initiative to devise a homemade apparatus which is suitable for babies of the smallest size. It must be emphasized that cyanosis should not be a deterrent to operation, since the administration of a gas containing a high percentage of oxygen will improve the baby's color, and the operative removal of the abdominal viscera from the chest will also facilitate the child's breathing efforts. It is unnecessary to use an intratracheal tube; indeed, this is apt to be followed by troublesome edema of the larynx in the ensuing twenty-four hours. Only a tightly fitting mask, without an intra-tracheal tube, was used for all of the patients reported on here.* [98]

CDH was considered a surgical emergency [99] and immediate operation was recommended once the diagnosis had been made—especially if respiratory distress was present. A case report from 1950 [100] demonstrated the extent to which improvisation was employed to facilitate urgent surgery. The child was 5 days old and in considerable respiratory distress and required oxygen at all times—a decision was made to perform immediate surgery. "Ether was the anesthetic agent of choice. The equipment at hand was a small open mask, an infant-sized metal oral pharyngeal airway, a rubber infant-sized mask from a Kreiselman resuscitator, a socket elbow, a short corrugated tube section, a Peterson ether drop cup, and for a breathing bag a toy red rubber balloon." During the procedure, the two red rubber balloons that were available both disintegrated due to contact with liquid ether and were replaced by rubber condoms! To the credit of the team, the infant survived.[3]

In the 1950s, the association between pulmonary hypoplasia and CDH was reported [101]. From this time and into the 1960s, improvements in the care and transportation [102] of critically ill neonates resulted in more infants with CDH presenting for emergency surgery. Many of these who would have died without surgery now died postoperatively secondary to their pulmonary status. The high mortality rates associated with repair CDH stimulated many investigators and clinicians and attention turned to means to optimize pulmonary function postoperatively. These means included various patterns of controlled ventilation and measures to reduce pulmonary vascular resistance (PVR) [103]. The thought developed that the cause of death in some cases was not simple hypoplasia but potentially reversible changes in PVR [103]. The standard approach to anesthesia for CDH at this

[3] The other obvious question that this case raises is whether the reporting institution was the most appropriate place to be performing this surgery. However, in 1950, the concept of regionalization of pediatric and neonatal services was undeveloped even in Europe and was largely unrecognized in North America.

time, no bag and mask ventilation, endotracheal intubation, avoidance of N_2O, and care to avoid large positive pressures, was augmented by steps to control PVR if required.

One problem that had complicated the management of the infant with CDH was that some experienced very few problems postoperatively, whereas others were desperately ill. Hence, there was great interest in identifying those prognostic factors that determined which infants would require aggressive invasive measures. Raphaely and Downs in Philadelphia developed a scoring system based on the preoperative and postreduction alveolar/arterial oxygen tension gradient [104]. Desmond Bohn and his colleagues in Toronto suggested a system to predict the extent of pulmonary hypoplasia based on the preoperative arterial CO_2 tension and a ventilatory index (mean airway pressure x ventilatory rate) [105]. Bohn et al. also suggested that consideration should be given to an initial nonsurgical approach to CDH in the expectation that impaired pulmonary function not due to hypoplasia might improve [105]. In the same year, 1987, another study from Toronto had shown that surgical repair of CDH impaired rather than improved respiratory mechanics [106]. Thus, CDH management evolved from a surgical emergency into a potential complex management problem for the neonatal intensivist, sometimes involving preoperative ECMO therapy. Surgery was now performed only when the respiratory status was improved.

Abdominal Wall Defects

Reports of exomphalos (omphalocele) are found in medical writings from the middle ages onward, but the infants generally soon died—usually of peritonitis. There are a few instances where conservative treatment using antiseptic preparations applied to the lesion resulted in granulation tissue formation and epithelialization with survival. Operative treatment before the 1940s was usually fatal [107]. Successful surgical treatment was reported in 1948 [108], and in 1951, a further successful case was reported in which the anesthetic used "was sugar and whisky administered on a small gauze nipple" [109]. The postoperative course was complicated by peritonitis; however, the patient recovered and was discharged on the 75th postoperative day. Much credit for the recovery was given to the use of prolonged intravenous fluid therapy. At this time, it was recognized that omphalocele was often associated with other significant congenital malformations. It was also noted that the immediate prognosis depended on whether the membrane covering the viscera was intact or ruptured; in the latter case, a fatal result was certain [110]. In 1953, a successful case is recorded in which open ether was administered for anesthesia: "*The bowels were returned to the abdominal cavity with difficulty, and the wound was closed in a single layer. The anaesthesia must be sufficiently deep to relax the abdominal muscles. This requires the services of a skilled anaesthetist*" [110]. It was suggested that a stomach tube should be in place to aspirate secretions as the bowel was reduced into the abdomen—obviously a serious concern when an open technique was used.

By the 1970s, the problems of heat conservation, fluid therapy, prevention of infection, and prolonged postoperative ileus were recognized and being managed [111]. Local analgesia infiltrated by the surgeon was still quite frequently utilized "with anesthesia standby." This led to cautions in the 1979 edition of the Manual of Pediatric Anesthesia [112]: first, to monitor how much local analgesic the surgeon injected and, second, to consider intubating the airway—to protect it against aspiration of regurgitated stomach contents. The introduction of endotracheal intubation and controlled ventilation greatly facilitated general anesthesia management but introduced the problem of determining whether the infant could tolerate the increased intra-abdominal pressure (IAP) postoperatively. Controlled ventilation could be continued postoperatively, and simple closure of the skin only and delayed closure using Silon pouch were options. However, it was appreciated that increased IAP not only impaired ventilation and circulation but also severely compromised splanchnic and renal perfusion. In 1989, Yaster et al. suggested that the intragastric pressure (IGP) and/or central venous pressure (CVP) should be monitored during replacement of the viscera; IGP in excess of 20 mm/Hg or CVP increases of 4 mm/Hg are unlikely to be tolerated [113].

By the end of the twentieth century, prenatal diagnosis and progress in anesthesia management, critical care, and intravenous alimentation resulted in significantly reduced mortality and morbidity. The mortality rate for gastroschisis was under 10% and the mortality in cases of omphalocele was largely dictated by the presence or absence of associated malformations.

Neonatal Cardiovascular Surgery

Surgery of the heart and great vessels was introduced in the 1940s and 1950s, but initially, very few of the patients were neonates. Robert Gross ligated a persistent ductus arteriosus in a child in 1939 and launched pediatric cardiovascular surgery. Most of his early patients were older but he did describe division of vascular ring in patients that included a 3-week-old infant in 1951 [114]:

> *Anesthesia in all these subjects has been with a closed system, using ether or cyclopropane. In all cases, an intratracheal tube, preferably of soft polyethylene, has been employed. Such a tube is essential for the maintenance of an adequate airway, particu-*

larly in the first four types of anomalies just described, in each of which the trachea is markedly narrowed and an adequate exchange might not be obtained until a tube is passed down beyond the obstructed point. [114]

William Mustard in Toronto operated on neonates with preductal coarctation of the aorta in 1953 [115] with long-term success. The anesthetic regimen was: "*Induction is with pentothal 5 mg per pound and syncurine 0.01 mg per pound mixed together in the same syringe. Orotracheal intubation is performed after succinylcholine 1 mg per 5 pounds. The patient is maintained on a 50–75% nitrous oxide with oxygen mixture, and control of ventilation is maintained by means of frequent small doses of succinylcholine*" [115]. The anesthetics were all administered by Dr. Code Smith who first described the esophageal stethoscope [116], developed in order to monitor heart and breath sounds reliably during thoracic surgery in small infants.

Open Heart Surgery

The use of open heart surgery with cardiopulmonary bypass (CPB) in neonates was initially associated with very high mortality rates. In 1963, it was stated "It is apparent that perfusion can be performed on even the smallest infants. It is equally certain that present methods of perfusion in small infants are hazardous and should be applied only in extraordinary circumstances" [117]. The authors reported a mortality rate of 66% for infants of 0.2 square meters body surface area. The mortality was considered related to the severity of the CHD and to postoperative complications related to the "marginal status of the infant's cardiopulmonary system" [117] There were, however, also frequent technical problems related to the small size of the patients. The problems of applying CPB to the smaller infants stimulated an interest in performing surgery under deep hypothermic circulatory arrest (18–20 °C) using only surface cooling and rewarming [118]. The technique originated in Japan but was adopted by several centers in North America. Anesthesia was maintained using diethyl ether, which was thought to protect against ventricular fibrillation during the cooling phase [118]. Using this technique, an overall mortality rate of 42% was reported [118]. As techniques for CPB rapidly evolved, and as flammable ether was considered an unacceptable hazard by many groups, cooling of neonates on bypass became more common.

Profoundly hypothermic circulatory arrest (PHCA) was first used in neonates in the 1960s and became widely used thereafter. Intra-atrial repair was simplified in the absence of venous cannulae. However, controversy soon emerged concerning the long-term safety of PHCA versus continued perfusion [119]. There was also much debate concerning the optimal management of the pH status and other variables (e.g., hematocrit) during cooling bypass [120].

Regional Analgesia

Bier popularized spinal analgesia in 1898, though Corning had successfully used the method 15 years earlier. The use of spinal analgesia in a neonate 24 h old with acute intestinal obstruction due to congenital hernia of the umbilical cord was described in 1912 [121]. The method used was that of Dr. Tyrell Gray, at that time medical superintendent at the Hospital for Sick Children, Great Ormond Street, who had written extensively on the subject of spinal anesthesia in infants and children [122]. The drug used was Stovaine (0.012G) with glucose. Stovaine (amylocaine) was the first synthesized local anesthetic and was widely used for spinal anesthesia being less toxic than cocaine. The dose used would produce anesthesia for up to 1 h. Reports of the use of spinal analgesia for abdominal and perineal surgery in infants are found from several centers during the first half of the twentieth century.

In the 1960s, an interesting series of neonates with open myelomeningocele underwent corrective surgery after direct injection of local analgesic into the lesion by the surgeon [123]. A solution of 1% lidocaine was used and produced anesthesia very adequate for the repair—which was always completed in less than one hour. No complications were noted and the decrease in blood pressure after the injection was small. The rationale for the use of this technique was that it was less hazardous than general anesthesia administered by an inexperienced anesthetist.

Spinal anesthesia for preterm neonates with inguinal hernia became popular late in the twentieth century when it was suggested that postoperative respiratory complications were less common than after general anesthesia [124]. Studies also confirmed that the effect of a spinal block on the blood pressure is relatively minor in small infants [125]. There was also renewed interest in some centers for the use of spinal anesthesia for abdominal and even thoracic surgery.

As has been mentioned throughout this chapter, infiltration of local anesthetics was often employed for the neonate. In 1930, Denis Browne, the surgeon at Great Ormond Street Hospital, described a restraint for the small infant that could be used during local or general anesthesia (Fig. 1.2) [126]. This was widely used in Britain for many years, and he wrote of it: "In operating on babies there are certain special difficulties. Owing to their light weight and powers of contortion

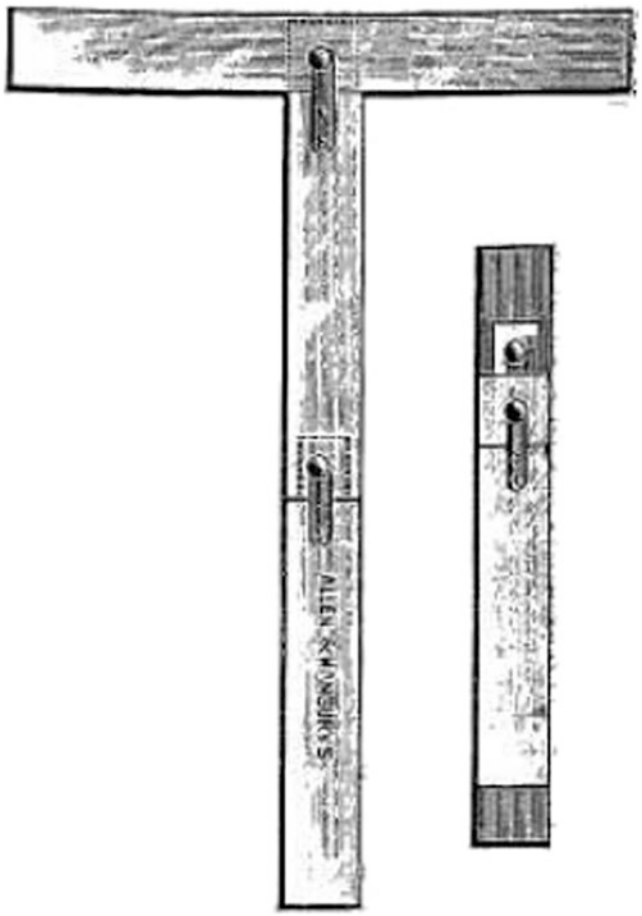

Fig. 1.2 The Denis Browne crucifix

they need careful holding for greater or less time, according to the type of anaesthetic, and their small size makes it difficult for the holder to avoid the operators. In work on these cases, both as operator and anaesthetist, I have found great help in a simple device which holds the child firmly, prevents chilling, and permits the use of local anaesthesia or the minimum of general. It is a 'crucifix,' the original model of which was a simple T of 2-inch wood, the cross limb 18 inches long and the main one 24 inches. As this was awkward to carry and had an inauspicious look about it when taken into a private house, I devised a collapsible model in duralumin, with a sponge rubber padding, and this has been very satisfactory" [126].

Minimally Invasive Neonatal Surgery

During the final decades of the twentieth century, advances in techniques and technology made it possible to apply minimally invasive/endoscopic surgery to very small infants. Closure of persistent ductus arteriosus by inserting an intravascular balloon was performed in an infant in 1979 [127] and by thoracoscopic clipping of the ductus in a preterm infant in 1993 [128]. Regarding endoscopic abdominal surgery, extramucosal pyloromyotomy was described in 1991 in a series of 70 infants [129]. Peritoneoscopy of infants for diagnostic purposes had been performed since 1972 [130]. The physiological effects on the neonate of abdominal distension by carbon dioxide and the problems of facilitating intrathoracic endoscopic procedures were soon described and discussed [131]. Very early in the twenty-first century, thoracoscopic repair of tracheoesophageal fistula was reported [132]. By 2014, it could be stated that many surgical procedures for the neonate could be performed by minimally invasive techniques [133]. Significantly, these techniques reduce the stress of the surgical procedure and short-term morbidity [133] and eliminate the risk of some delayed complications, for example, post-thoracotomy scoliosis [134].

Ex Utero Intrapartum Treatment: "The EXIT Procedure"

The "EXIT Procedure" was described in 1997 as a means to maintain the newly delivered infant on the placental circulation until pulmonary ventilation could be established. The first indication for this was to provide time for the surgical removal of tracheal clips which had been placed to stimulate lung growth in cases of diaphragmatic hernia [135]. Subsequently, the technique has been applied to manage infants with various congenital airway obstructive lesions. Anesthesia management for the mother and infant was developed to ensure continued placental blood flow to the infant, maximize placental gas exchange, and provide uterine relaxation [136]. Most recently, the technique has been applied to permit EXIT to ECMO management of infants with potentially disastrous congenital cardiac anomalies.[137]

Regionalization of Neonatal Services

Real progress in modern neonatal surgery commenced in 1945 after World War II. In 1949, there were 58 neonatal operations at the Hospital for Sick Children in London and 27 (46%) of these infants died [138]. These results and similar figures from the Alder Hey Hospital in Liverpool led Peter Rickham to write "If in this country we are to improve the chances of survival of children born with congenital malformations an efficient neonatal surgical service must be organized" [138]. At this time, congenital malformations were listed as the third most common cause of neonatal death in the USA, but there were three centers (Boston, Philadelphia, Chicago) where Rickham observed very good results for neonatal surgery: "Surgical management and technique differed very little. American neonatal anesthesia was definitely

inferior to that in Liverpool, many operations being done under local or ether anesthesia. The important difference was the postoperative management. There were more highly trained medical personnel and nurses in the American Hospitals providing a highly efficient round the clock service…."

Mr. Rickham went on to act as a prime mover in the establishment of the "first neonatal unit in the world" which opened in 1953 at the Alder Hey Children's Hospital [139]. In the last half of the twentieth century, regionalization of neonatal services progressed steadily in Great Britain and in other European countries. The standards for the staffing and equipping of neonatal units and the organization for the transport of patients to these units are rigidly controlled. The concentration of patients in a few units ensured that the medical and nursing staff could gather the experience necessary to ensure optimal outcomes for their patients while providing training for the next generation of care providers. In Canada, complex neonatal surgery has been largely concentrated within the children's hospitals which are situated in most provinces, and thus, a similar regionalization has been achieved.

In the USA, regionalization of neonatal services and the establishment of units to serve all regions with an associated high volume of patients has been less consistent. There are many geographic problems involved, and there has also been a desire by many smaller hospitals to have a neonatal unit and to provide pediatric surgical services. This has sometimes led to problems with providing an adequate pediatric case load for credentialing purposes [140] and might indeed sometimes compromise results. In many states, however, neonatal emergency transport systems have been effective in directing a high volume of patients to regional neonatal surgical units [141]. The American Academy of Pediatrics in 2002 formulated and published general guidelines for referral of patients with major congenital anomalies to pediatric surgical specialists [142].

Research in Neonatal Anesthesia

Before 1960 very little research was conducted, those anesthetizing infants were busy with their clinical work [143], and anesthesia methods were largely based on what had worked in the experience of practitioners and their teachers. However, early investigations into the pharmacology of the anesthetic drugs in the neonate were commencing. Stead in 1955 reported the effects of neuromuscular blocking agents in the neonate [144]. Rackow and Salanitre studied the pharmacokinetics of the inhaled anesthetics in infants and reported these in 1969 [145]. The volatile anesthetic dose requirements for the neonate were the subject of some confusion until more precise studies in tightly controlled age groups were carried out in the 1980s [146]. Similar studies in preterm infants were conducted by Ledez and Lerman shortly thereafter [147]. As the numbers of pediatric anesthesia subspecialists swelled in the last decades of the twentieth century, there was a corresponding increase in research output and a more scientific approach to neonatal anesthesia became a reality. This did, however, require a closer evaluation of the ethics of performing studies in infants [148] and indeed the ethics of providing anesthesia for infants.

Ethical Considerations and Infant Anesthesia

The suggestion that the administration of anesthesia to infants might have long-term adverse consequences has been raised. In the 1970s, it was suggested that the incidence of asthma and respiratory allergies might be increased in children who were administered anesthesia in infancy [149]. A subsequent study failed to corroborate this association [150]. Late in the twentieth century, learning disabilities were described in children who had general anesthesia in infancy [151]. However, a study in more than 1100 identical twins in the Netherlands demonstrated that in discordant twins (i.e., one had an anesthetic and the other did not), the IQ values in each pair were identical in a 10-year follow-up [152]. Concerns were also raised by numerous neonatal animal studies that suggested that most general anesthetic agents are toxic to the developing brain [153]. Despite many studies [154–156], it has not been proven that exposure of human neonates to a well-conducted general anesthetic has significant adverse effects [157]. It has, however, been demonstrated that inadequately treated pain during infancy results in both short-term and long-term adverse effects [158]. Repeated anesthesia may be associated with adverse neurocognitive outcomes but many perioperative factors other than the use of an anesthetic drug are present in such patients [157]. Currently, the preponderance of evidence supports the ethical path of administering anesthesia to prevent pain and modulate the physiological responses to surgery in neonates. The problem for the anesthesiologist is to communicate these thoughts clearly to anxious parents who may have been exposed to less reliable information in the media. Indeed, parents have every right to be confused. In the 1980s, newspaper headlines screamed about newborn infants being subjected to surgery without effective anesthesia [159]; more recently, these same newspapers now warn that anesthesia drugs may harm those same patients [160].

The future path for pediatric anesthesiology is to pursue the ideal of perfecting agents and techniques that will cause the least harm and ensure the greatest benefits for our precious neonatal patients. Progressively, we have been able to practice evidence-based neonatal anesthesia management. The full history of neonatal anesthesia cannot yet be written—but the future may be just as exciting as was the past.

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Physiology and Development of the Term and Preterm Neonate

2

Claire Brett and David Robinowitz

Perinatal injury, prematurity, and/or congenital anomalies inflict profound long- and short-term physical, psychological, emotional, social, and financial stresses on survivors, their families, and society. Both the Annual Summary of Vital Statistics (2013–2014) [2] and the National Vital Statistics Reports (2017) [1] list "disorders relating to short gestation and low birth weight" as the second leading cause (~18%) of infant death, second only to congenital malformations, deformations, and chromosomal abnormalities (~20%). In the United States in 2014 [2], 9.57% of the 3,988,076 live births (381,659) were preterm (<37 weeks' gestation), 8.0% (319,046) were low birth weight (<2500 g), 6.6% (263,213) were moderately low birth weight (1500–2499 g), and 1.40% (55,833) were very low birth weight (<1500 g).

Although birth rates decreased 13% between 2009 and 2016, the rate of preterm birth increased from 9.57% in 2014 and 9.63% in 2015 to 9.85% in 2016. Of the preterm births, the early preterm birth rate remained steady (2.76%) over this period, whereas the late preterm rate (34–36 weeks' gestation) primarily accounted for the difference, increasing from 6.82% in 2014 to 7.09% in 2016 [3]. In fact, 75% of preterm infants are late preterm [4].

In 2014, 56.9% of all infant deaths could be attributed to five causes: congenital malformations (20%), short gestation and low birth weight (18%), neonates affected by maternal complications of pregnancy (6.8%), sudden infant death syndrome (6.7%), and accidents (5.0%). The etiology of neonatal death (<28 days) differs from that for infants (>28 days to 1 year). For example, in the neonate in 2015, sepsis, respiratory distress of the newborn, neonatal hemorrhage, necrotizing enterocolitis, and birth asphyxia contributed to neonatal mortality, whereas sudden infant death syndrome did not [1].

Mortality during the first year of life for late preterm infants (34–36 weeks' gestation) is threefold greater than for full-term infants, often related to a combination of intrapartum events (e.g., placental and umbilical cord injury) and postnatal complications (e.g., respiratory problems, sepsis, and metabolic instability such as hypoglycemia and hypothermia) [5]. Recently, late–moderate preterm infants (32–36 weeks' gestation) exhibited approximately twice the risk for neurodevelopmental impairment at age 2 years, primarily in the cognitive domain, compared with full-term neonates. Male sex, socioeconomic disadvantage, and preeclampsia were identified as independent predictors of low cognitive scores in this cohort [6]. The morbidity and mortality associated with late preterm infants are particularly stunning because approximately 8% of all births [3] and 75% of preterm infants are 34–36 weeks' gestational age [4, 5]

The management of extremely low birth weight (ELBW) infants (<1000 g), especially those born near the limits of viability (gestational age between 22 and 24 weeks), continues to receive intense scrutiny, primarily because of the large risk for death and adverse neurodevelopment. A prediction model of survival of preterm infants developed in England (East Midlands and Yorkshire regions) using gestational age, birth weight, and gender in preterm infants showed increasing survival from 27.7% (boys) and 34.5% (girls) at 23 weeks to >99% (boys and girls) at 32 weeks [7]. Several reports noted that a decrease in short-term complications lagged behind the improved survival of ELBW infants [8–11]. More recently, reports note that mortality has decreased and neurodevelopmental outcomes improved slightly, but progress has not been dramatic. For example, the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network reported that the percentage of infants (gestational age 22–24 weeks) who survived without neurodevelopmental impairment increased from 16% (2004–2007) to 20% (2008–2011), whereas the percentage of infants who survived with neurodevelopmental impairment did not change significantly (15%, 2003–2007; 16%, 2008–2011). [12] Data from Japan describe the incidence of

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death or neurodevelopmental impairment as 80%, 64%, and 39% in infants after 22, 23, and 24 weeks' gestation, respectively [13]

Major morbidities (e.g., chronic lung disease, retinopathy of prematurity) and direct injury to the brain (intraventricular hemorrhage or periventricular leukomalacia) predict death or survival with significant neurodevelopmental impairment [14, 15]. The incidence of poor outcomes at 18 months is doubled, tripled, or quintupled when 1, 2, or 3 of these morbidities, respectively, are encountered [15]. Infection (sepsis, meningitis) seems to inflict less of an impact on outcomes than the three major morbidities. Intrauterine and early postnatal events impact long-term survival, health, and function. Developing strategies to prevent preterm birth and devising interventions to treat anomalies both in utero and postnatally remain strategic priorities.

Over the last two decades, a significant epidemiology-based literature has suggested the importance of the "developmental origins of health and disease." That is, an environmental insult (e.g., over- or undernutrition, infection, psychological stress) during a critical period of fetal or early postnatal development may "program" long-term physiologic, structural, and epigenetic changes that increase the risk for various diseases in adulthood. In his initial study, Barker correlated increased mortality from coronary disease with low birth weight in a cohort from Hertfordshire, United Kingdom [16]. His "thrifty phenotype hypothesis" (survival of the undernourished fetus demands that nutrition be directed to vital organs such as the brain, resulting in insulin resistance in other tissues such as the muscle and pancreas) [17, 18] provided a framework to suggest that an adverse fetal environment (e.g., chronic placental insufficiency) elicited an adaptive response to protect critical organs such as the brain and heart at the expense of other sites (e.g., kidney) that involve long-term physiologic reprogramming [19–21]. Such reprogramming is associated with risk for hypertension, type II diabetes, and hyperlipidemia, which predispose to the metabolic syndrome and cardiovascular disease [22–26]. Of note, the most significant glucose intolerance has been correlated with low birth weight combined with rapid postnatal weight gain [27, 28]. Recently, based on a cohort of ELBW subjects from Canada (born 1977–1982), a group of adults was noted to have a fourfold increased risk of developing dysglycemia by their fourth decade of life. Increased adiposity and reduced lean mass for height accompanied the dysglycemia [29].

In addition to long-term metabolic effects, restricted intrauterine growth has been associated with a reduced number of nephrons, a recognized pathway to renal failure, and hypertension. Similar to intrauterine growth retardation, preterm birth is associated with an apparent arrest of nephron growth and later hypertension and insulin resistance [30, 31]. Similarly, linking adult lung disease to perinatal insults such as intrauterine growth restriction, preterm birth, exposure to environmental toxins, or dietary deficiency during critical periods of fetal development has been increasingly appreciated both from epigenetic factors [32], genetics, and other host susceptibilities [33–35]. That is, in many cases, the origins of asthma and COPD can be traced to fetal and early postnatal life [33, 35, 36]. One concept suggests that insults during prenatal and early neonatal life (especially the first year) impede normal structural and functional maturation so that peak lung function is never achieved, exaggerating the normal age-related decline in lung function [33] beginning in the second to third decade of life. In part, this may evolve secondary to greater susceptibility to infectious and environmental toxins during infancy and childhood and continuing into adulthood.

Thus, the "thrifty phenotype hypothesis" shifted to a "developmental plasticity" theory [37, 38], which captures the effects of a wider variety of early derangements on risk for diseases in adulthood, including small-for-gestational-age [39], large-for-gestational-age [40], and preterm infants [41–44]. The initial report from Barker has spawned an entire research focus and model, the "developmental origins of health and disease" [38, 45–47]. The full impact of and/or synergistic role of "the thrifty phenotype" and/or "developmental plasticity" on the well-established lifelong diagnoses associated with preterm birth and congenital anomalies continues to evolve.

Cardiovascular Function

The Transitional Circulation

The abrupt shift from fetal to postnatal life demands drastic and prompt changes in cardiopulmonary physiology. The fetal circulation is characterized by increased pulmonary vascular resistance, decreased pulmonary blood flow (Fig. 2.1), decreased systemic vascular resistance, and right-to-left blood flow through the patent ductus arteriosus and the foramen ovale (Fig. 2.2). In utero, the return of blood to the heart is derived from both the fetal and the placental circulations. Similarly, blood distributed to organs and the placenta from the heart is derived from both ventricles. Thus, the fetal circulation is not in series as it is in the adult. Furthermore, in utero, volumetric outputs from the right and left ventricles differ. Therefore, cardiac output is expressed as the combined ventricular output, the total volume ejected by the two ventricles. For example, in fetal sheep, in late gestation, the right ventricle ejects 300 mL/min/kg (or 66% of the combined ventricular output) compared with 150 mL/min/kg (or 33% of the combined ventricular output) from the left ventricle [48]. Estimated with Doppler ultrasound, the combined ventricular output in human fetuses is similar (range, 410–503 mL/kg/min) [49].

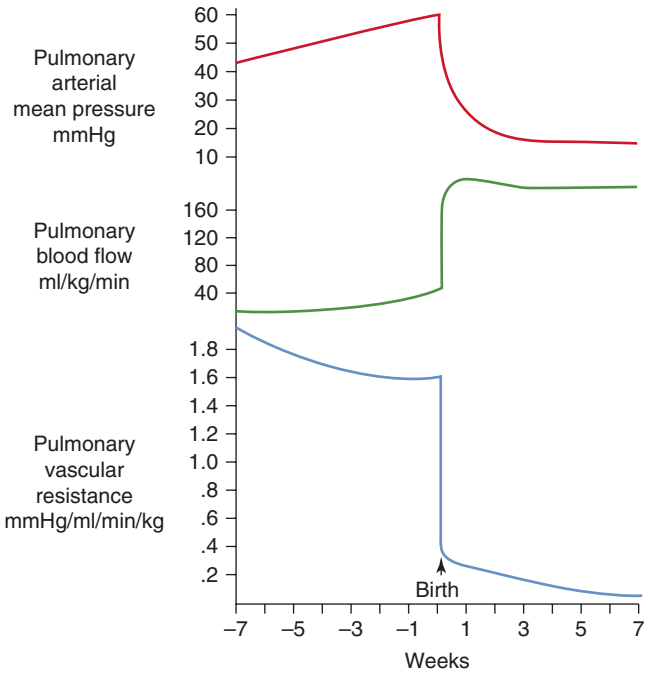

Fig. 2.1 The fetal circulation is characterized by high pulmonary arterial mean pressure and pulmonary vascular resistance and low pulmonary blood flow. At birth, the dramatic decrease in pulmonary vascular resistance is accompanied by a parallel decrease in pulmonary arterial blood pressure and an increase in pulmonary blood flow. Of note, the pulmonary vascular resistance gradually decreases further over the first 6 weeks of life (from [52])

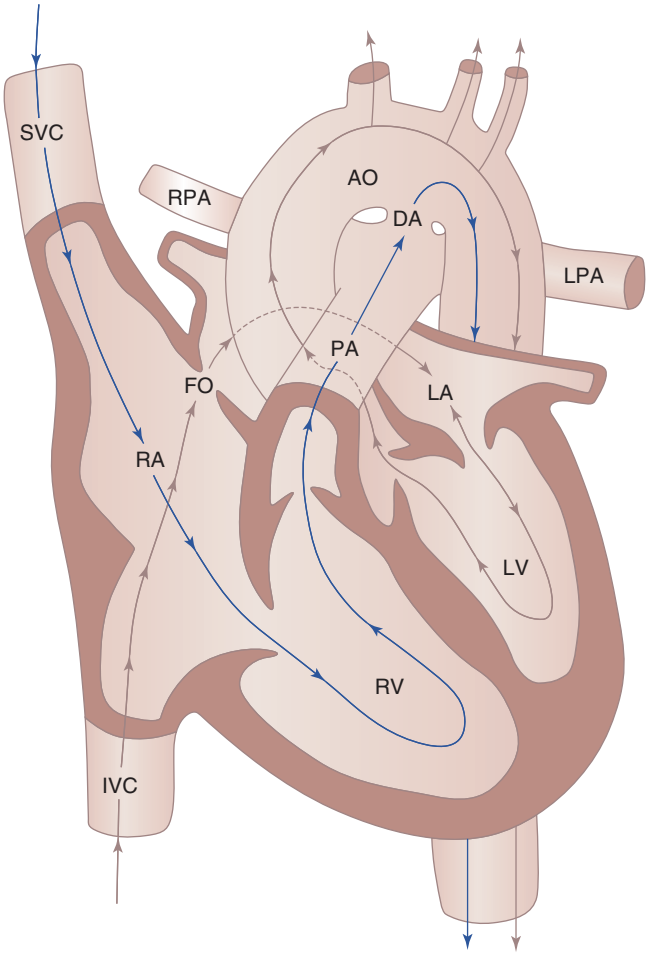

Fig. 2.2 The fetal circulation. Desaturated blood from the superior vena cava preferentially flows into the right ventricle, into the pulmonary artery, across the ductus arteriosus, and to the descending aorta to the placenta. Relatively well-saturated blood from the ductus venosus enters the inferior vena cava and preferentially crosses the foramen ovale to the left atrium, the left ventricle, and the cerebral circulation (from [53])

However, the distribution of the combined ventricular output between the right and left ventricles, respectfully, differed throughout gestation (at 20 weeks, 53% vs. 47%; 30 weeks, 57% vs. 43%; 38 weeks, 60% vs. 40%) [50]. During the same periods, flow via the foramen ovale decreased from 34% (20 weeks) to 18–19% (30–40 weeks) [50]. In contrast, in another study, although reporting a similar combined ventricular output (425 mL/kg/min) in human fetuses, the value did not vary as a function of gestation. The ratio of fetal right (59%) to left ventricular output (41%) also remained unchanged throughout gestation (13 weeks to term) [49]. In the human fetus, blood flow through the ductus venosus decreases between mid-gestation (30% of umbilical blood flow) and 30 weeks (20% of umbilical flow). This flow is variable among subjects but without dramatic changes in late pregnancy. The physiologic implication of reduced blood flow after 30 weeks' gestation is unclear [51]. On the other hand, examining flow in the ductus venosus via Doppler has been incorporated into clinical care to monitor fetal well-being (e.g., growth retardation, congenital heart disease, hydrops fetalis) by evaluating the adequacy of placental flow, in some cases to determine the timing of delivery.

The umbilical vein enters the hilum of the liver where it divides into three branches: vessels that provide flow directly to the left lobe, a large arcuate branch that joins the portal vein to supply the right lobe, and the ductus venosus that proceeds cephalad to join the inferior vena cava (Fig. 2.3). Umbilical venous blood flowing into the inferior vena cava via the ductus venosus is preferentially directed across the foramen ovale into the left atrium and then the left ventricle. Thus, highly oxygenated blood exits the placenta, bypasses the liver, and flows directly to the myocardium and brain. Desaturated blood from the superior vena cava and the abdominal vena cava enters the right atrium and ventricle and then returns to the placenta after crossing the ductus arteriosus. A variety of anatomic features of the atrial septum (e.g., crista dividens, eustachian valve) and the angle of entry of the ductus venosus into the inferior vena cava facilitate this preferential streaming [48].

Pulmonary blood flow increases during mid-gestation (20–30 weeks) in the human fetus as pulmonary vascular

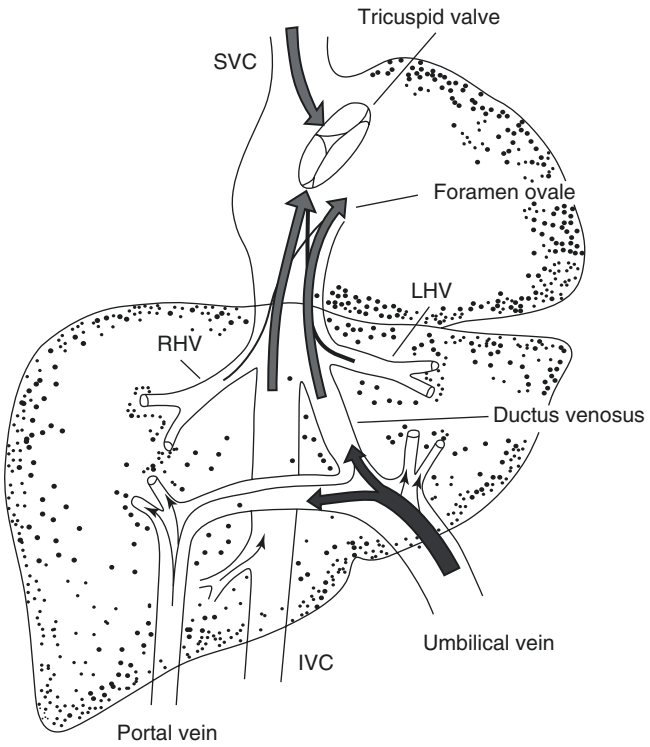

Fig. 2.3 The fetal circulation. The blood from the umbilical vein that enters the ductus venosus preferentially streams across the foramen ovale to enter the left atrium and ventricle and the cerebral circulation (from Rudolph [54])

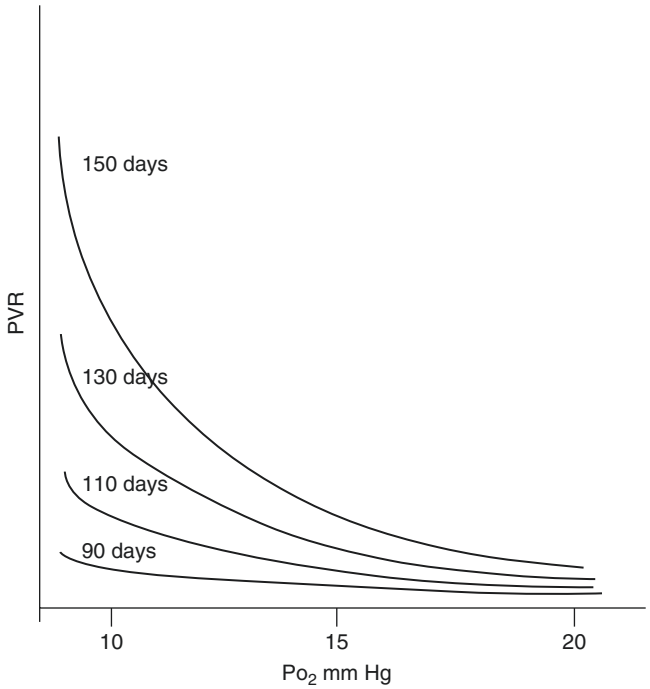

Fig. 2.4 Response of the fetal pulmonary circulation to hypoxia (fetal lamb). With advancing gestation, the response of the pulmonary circulation to decreasing oxygen saturation becomes more pronounced (from Rudolph [57])

resistance decreases. In addition, the proportion of the combined ventricular output allocated to pulmonary blood flow increases from ~13% of the combined ventricular output at mid-gestation to 25% at 30 weeks, without further change in the third trimester; pulmonary vascular resistance decreases 1.5-fold [50]. These values contrast with those from the classic studies in lambs where pulmonary blood flow was <10% of the combined ventricular output (late gestation) and with one study in human fetuses that also noted that in utero pulmonary blood flow was small (~11%) and did not change between 13 and 41 weeks' gestation [49]. The pulmonary vascular resistance of human fetuses responds to the administration of oxygen to the mother ($FIO_2 = 0.60$) after 31 weeks' gestation [55]. Similar studies in fetal lambs documented that the fetal circulation is briskly responsive to both hyperoxia and hypoxia and that these responses are greater in late gestation (Fig. 2.4) [56]. Vasomotor control of the pulmonary circulation in utero, however, may be disturbed in the presence of a congenital heart defect in which oxygen delivery to the lungs may be abnormal (e.g., aortopulmonary transposition) thereby dramatically affecting the development of vessel morphology [57]. At birth, when the placenta separates, pulmonary vascular resistance decreases dramatically, and pulmonary blood flow increases in response to the rapid increase in oxygen tension and the onset of alveolar ventilation (Fig. 2.1). Simultaneously, both systemic vascular resistance and left atrial pressure increase, eliminating the right-to-left shunting through the foramen ovale. Bidirectional shunting through the ductus arteriosus may continue in the normal full-term infant during the first 48 h of life. With normal transition, distinct and separate pulmonary and systemic circulations are established.

Postnatally, the marked vasoconstrictor responses of the pulmonary circulation to hypoxia persist, and pulmonary vascular resistance also responds significantly to changes in pH (Fig. 2.5) [58]. In part, this reactivity may be related to the persistent high pulmonary vascular resistance during the first few weeks of postnatal life compared with the older infant (Fig. 2.1). The reactivity of the pulmonary vasculature can be striking, and, in the neonate, arterial hypoxemia or acidosis can vasoconstrict the pulmonary arteries and induce pulmonary hypertension, thereby impeding forward blood flow and, by default, forcing right-to-left shunting through the foramen ovale and/or ductus arteriosus. This resembles the normal fetal circulatory pattern and, therefore is often termed persistent fetal circulation or persistent pulmonary hypertension of the newborn (PPHN) and further exacerbates the hypoxemia and acidosis. The disorder has been divided into three types: maladaptation (structurally normal but abnormally constricted vessels due to parenchymal disease such as meconium aspiration, respiratory distress syndrome, pneumonia), maldevelopment (excessive muscular

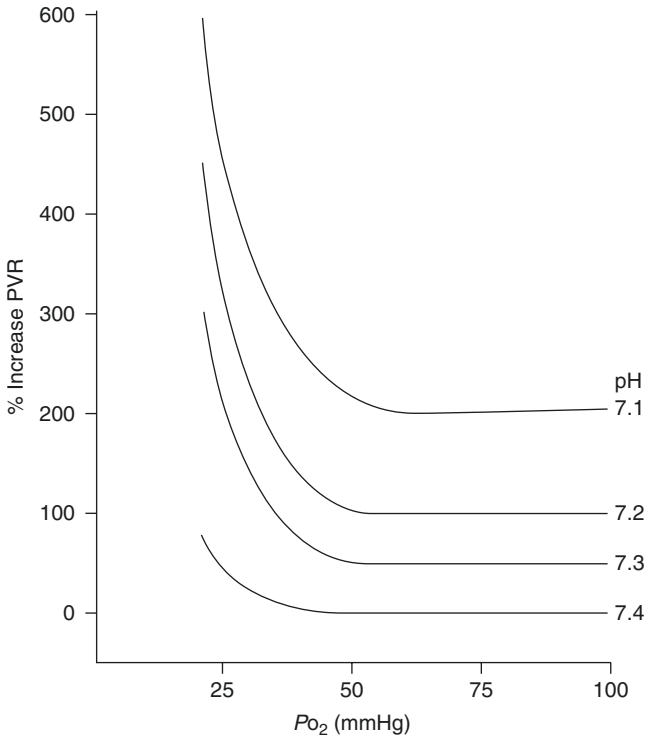

Fig. 2.5 Response of the neonatal pulmonary circulation to hypoxia and acidosis (lamb). The breakpoint for a marked increase in pulmonary vascular resistance in response to decreasing oxygen saturation is dramatically dependent on pH (used with permission from Rudolph and Yuan [58])

development in the pulmonary vessels), and underdevelopment (hypoplasia, as with congenital diaphragmatic hernia) [59]. An echocardiogram is routinely performed in infants manifesting signs and symptoms of persistent pulmonary hypertension to definitively exclude structural cyanotic heart disease [60].

Although the control of the pulmonary circulation, especially during the transition from fetal to postnatal life, is complex and depends on the interaction of a variety of mediators and factors, receptors, and neurologic, endocrine, and vascular control mechanisms, nitric oxide (NO) plays a critical role in mediating the vasodilating effect of oxygen [61] via the (NO)-cyclic guanosine monophosphate pathway [59]. Another major pathway regulating pulmonary vascular tone includes the prostacyclin-cyclic adenosine monophosphate pathway [59]. Both act by decreasing the concentration of intracellular calcium. Other mechanisms contribute (e.g., oxygen-sensitive K^+ channels in pulmonary vascular smooth muscle) [62]. Despite the enormity of the research that has been focused on this topic, no single factor has yet been identified as the primary trigger responsible for the initiation of pulmonary vasodilatation at birth, nor is it clear whether the endothelial cell or the smooth muscle cell is the prime target [63].

A wide range of therapies and agents (ventilation, vasoactive agents) have been evaluated to treat PPHN, but the only selective vasodilator of the pulmonary circulation is NO. In many cases, inhaled NO induces a selective, rapid, and potent decrease in pulmonary vascular resistance without affecting systemic vascular resistance [63]. At low doses, toxicity is minimal. Unfortunately, up to 40% of infants with PPHN do not respond to NO. Moreover, although inhaled NO may provide short-term benefits (e.g., decreased need for ECMO), it has failed to reduce mortality, duration of hospitalization, or risk of neurodevelopmental impairment [64–67]). Similarly, effects as an antioxidant and an anti-inflammation agent (in animals) have been controversial [68]. Endogenous NO may have a role in alveolar and vascular development in the immature lung [69, 70] and, as a result, may be relevant in treating infants with bronchopulmonary dysplasia and other lung injuries [71]. However, the production and metabolism of NO are regulated on several levels, so that it is not surprising that its clinical effectiveness in both term and preterm infants remains controversial. For example, NO production depends on endothelial nitric oxide synthetase activity (eNOS; lung eNOS is type III). eNOS has both reductase and oxygenase domains. When its substrate l-arginine is available, oxidation of NADPH and NO synthetase produces NO. On the other hand, when the concentration of substrates or cofactors (e.g., heat shock protein 90) are reduced, NOS is uncoupled, and reactive oxygen or nitrogen species such as peroxynitrite are produced instead of NO. In fact, oxidative stress may contribute to the development of PPHN [72]. Similarly, the activity of soluble guanylate cyclase and cGMP-specific phosphodiesterase (PDE5) on smooth muscle cells potentiates the effectiveness of NO in augmenting cGMP production. PDE5 hydrolyzes cGMP, which controls the duration and magnitude of cGMP's effect.

Understanding the mechanisms for pulmonary vasoactivity should be the basis for clinical therapy. That is, oxygen, inhaled NO, and other relevant agents continue to evolve. Although oxygen is a potent pulmonary vasodilator, an inspired concentration in excess of 0.50 does not increase benefit [73]. Similarly, hyperoxia may induce oxidative stress and lung injury, counteracting any benefit of oxygen-induced vasodilation [74]. As a specific inhibitor of phosphodiesterase type 5 (PDE5), sildenafil decreases the metabolism of cAMP (i.e., inducing vasodilation) and has evolved as an adjunct to treat infants who fail to respond to iNO [75–77] as well as in the settings without access to iNO [78], with an impressive safety profile [79]. Similarly, milrinone (inhibitor of phosphodiesterase type 3 [PDE3]) decreases the metabolism of cGMP and serves as an adjunct to iNO to synergistically promote vasodilation [80], especially in the setting of left ventricular dysfunction. Inhaled prostacyclin (PGI_2) also targets the second major pathway (cGMP) to induce pulmonary vasodilatation, and its effectiveness seems similar to iNO [81], but more effective than oral sildenafil [76].

Distinct from both NO and prostacyclin, a molecule synthesized by the endothelial cell, endothelin-1 (ET-1) also exerts critical function in pulmonary vasoactivity. Bosentan and PGI_2 target the ET-1 pathway. The role of bosentan, a nonselective endothelin-1 receptor antagonist (endothelin A [vasoconstriction] and endothelin B [vasodilation]) remains incompletely defined, but one trial reported that it offered no benefit over NO [82].

In summary, a clear and effective therapy for PPHN remains elusive, in part related to the variation of associated clinical settings (i.e., intrauterine growth retardation, congenital diaphragmatic hernia, meconium aspiration, etc.). As novel therapies evolve (e.g., antioxidants, soluble guanylate cyclase activators, L-citrulline), the long-term outcome of infants with PPHN may be redefined.

The Placenta: In Utero Function and Cord Clamping

The fundamental and obvious role of the placenta is to ensure the health and well-being of the fetus. Recently, this organ has been increasingly scrutinized from additional perspectives, such as its regulatory function both for the mother (e.g., preeclampsia) and the fetus (prematurity, intrauterine growth retardation). By studying regulatory genes and other factors associated with the intense interaction of mother and fetus [83] that define fetal growth, immune competence, and in utero cardiovascular and hormonal/endocrine function, investigators have provided a preliminary framework for eventually intervening early in gestation to improve outcome [84]. In particular, a variety of markers released by the placenta may guide treatment and intervention during pregnancy. Development of an "organoid model" may allow an in vitro system to expand our understanding of the roles of this transient, but vital organ.

Of more immediate clinical relevance, the timing of umbilical cord clamping, the event that terminates the relationship of the fetus with the placenta, has been the subject of numerous investigations, clinical trials, and meta-analyses. The goals of these efforts center on optimally utilizing this organ during the immediate transition from fetal to extrauterine cardiovascular physiology.

The volume of blood available for transfusion to the neonate varies depending on the gestational age. At 20–32 weeks' gestation, the placenta receives approximately 33% of the fetal combined ventricular output or 110–120 mL/kg/min [85]. After 32 weeks, this distribution decreases to approximately 20% [86]. At birth, the blood remaining in the placenta may be critical to ensuring a smooth transition from fetus to neonate. In the term neonate, 20–35 mL/kg remains available to transfuse at birth [87], whereas in the preterm infant only 11–15 mL/kg [88] is available. Also, the volume of blood transfused correlates with the timing of clamping. Up to 50% of the transfusion is complete within 1 min and for the most part, it is completed by 5 min [85, 89].

Initially, "delayed clamping" and/or "milking" of the umbilical cord simply was recognized as a safe method to deliver the significant placental volume of red blood cells to the neonate. Although the data are inconsistent among studies, delaying cord clamping until after adequate pulmonary ventilation has been associated with a wide range of improved short- and longer-term outcomes, especially in preterm infants, including decreased mortality, greater hematocrit, and improved perinatal cardiovascular function/less need for inotropes [90, 91]. Data supporting advantages such as a reduced frequency of sepsis [92], necrotizing enterocolitis [93], and intraventricular hemorrhage [90–92] are less consistent. At the very least, this maneuver may promote a more physiologic transition from fetal to extrauterine life by avoiding the abrupt side effects of immediate cord clamping at birth.

Clamping of the umbilical cord occludes both the umbilical arteries (provides flow to the placenta from the descending aorta of the fetus) and the umbilical veins (provides flow from the placenta to the fetal heart). Clamping the umbilical cord after ventilation has been established provides two clear cardiovascular advantages to the neonate, especially the preterm neonate [94]. First, venous return to the heart (preload) abruptly decreases by as much as 40–50% because clamping the cord occludes the umbilical vein [95, 96]. Second, occluding the umbilical artery eliminates the low-resistance placenta and, therefore, increases the afterload to the left ventricle. This combination of decreasing preload at the same time that afterload increases may dramatically decrease cardiac output, challenging the neonatal myocardium during the transition from the fetal environment.

At birth, expanding and aerating the lung are the primary triggers that decrease the pulmonary vascular resistance and increase pulmonary blood flow. This pulmonary blood flow replaces umbilical venous return as preload to the left ventricle. The interrelated cascade of hemodynamic events at birth (i.e., closure of fetal vascular shunts, increased systemic and decreased pulmonary vascular resistances) separates the pulmonary and systemic circulations, enabling the right ventricle output to become the sole source for pulmonary blood flow; the pulmonary blood flow becomes the sole source of preload for the left ventricle. Thus, effective ventilation (spontaneous crying or assisted support) expands the fluid-filled fetal lung, dramatically increasing pulmonary blood flow (secondary to the dramatic decrease in pulmonary vascular resistance), preserving filling of the left atrium and left ventricular output. The interdependence of ventilation, establishing pulmonary blood flow, and timing of clamping of the umbilical cord directly impacts care during the third stage of labor [95]. For example, clamping the cord before

the lungs are expanded exposes the asphyxiated, hypoxic neonate to the added risk of an ischemic event (i.e., low cardiac output secondary to decreased preload plus increased systemic vascular resistance).

In summary, delayed clamping of the umbilical cord may contribute to a more physiologic transition to postnatal physiology by maintaining preload both by transfusion and allowing pulmonary blood flow to increase before eliminating umbilical venous flow. Although labor induces the release of catecholamines, renin, and angiotensin (i.e., contractions intermittently interrupt oxygen delivery) which may increase SVR, clamping the cord inflicts an even more dramatic effect because of the abrupt and dramatic increase in left ventricular afterload. The cardiovascular advantages of clamping the umbilical cord after the onset of breathing have been widely described in both preterm [97, 98] and term infants [99, 100]. In addition to the direct effects of the delayed clamping of the umbilical cord, tactile stimulation during the ~60-second (or longer) wait may induce infants to initiate spontaneous ventilation that stabilizes the neonatal circulatory transition, [91, 97, 101] which coincidently delays aggressive resuscitation.

In spite of robust publications, the definitive benefits versus risks of delaying clamping of the umbilical cord remain elusive. A recent Cochrane Review concluded that in preterm infants (<37 weeks' gestation), "increased circulating volume improves blood pressure, reduces the need for blood transfusion, risk of intraventricular hemorrhage and necrotizing enterocolitis" with no effect on mortality [93]. Similarly, a systematic review of preterm infants (<32 weeks' gestation) noted advantages to delayed cord clamping (or "milking of the cord") including a reduced rate of blood transfusion and intraventricular hemorrhage as well as reduced mortality [90]. In contrast, the Australian Placental Transfusion Study of preterm infants failed to identify advantages (mortality or major morbidity) of delayed compared with immediate cord clamping [102]. Similarly, the Cochrane Review, which focused on the need to establish ventilation before clamping the umbilical cord concluded that "a greater body of evidence is required … to answer the question of whether the intervention is or is not harmful" [103].

Finally, the most recent systematic review of preterm infants (18 randomized clinical trials) claims that delayed clamping reduced hospital mortality and the need for later transfusion, but without a difference in major morbidities (severe intraventricular hemorrhage, periventricular leukomalacia, chronic lung disease, patent ductus arteriosus, necrotizing enterocolitis, late-onset sepsis, and severe retinopathy of prematurity). Apgar scores and the need for resuscitation did not differ between the groups. Not unexpectedly, in some but not all studies [104], polycythemia and hyperbilirubinemia were more common in infants after the transfusion secondary to delayed clamping of the umbilical cord [91]. Maternal complications/morbidity (e.g., postpartum hemorrhage, need for transfusion) were not affected in any population. The primary advantage for term infants centers on increased hemoglobin concentration and iron stores, without effects on mortality or morbidity [105].

Given the limited risks from and complications of coupled with potential advantages associated with delayed umbilical cord clamping or "milking", the American Academy of Pediatrics [106], the American College of Obstetricians and Gynecologists [107], the World Health Organization [108], and the International Liaison Committee on Resuscitation [109] have published statements recommending "enhanced placental transfusion" [90, 110] (delayed cord clamping and/or "milking"), noting the need for additional data about benefits to define clinical guidelines. A consistent concern centers on the possible delay in initiating resuscitation, but this is more relevant to delayed clamping rather than to "milking" of the umbilical cord. Others argue that optimizing transfusion may decrease the need for resuscitation [90, 91, 97]. Furthermore, rather than setting a specific time or protocol, the clinical status of the neonate should dictate the approach toward clamping the umbilical cord [95].

Myocardial Development

Myocytes: Fetal and adult myocardia contract and relax similarly. That is, with activation, the cytosolic calcium concentration increases, inducing force generation, and as the cytosolic calcium concentration decreases, relaxation ensues. At all stages of maturation, the ventricle develops force against a varying resistance or load (contraction/ejection) followed by a period of relaxation (filling). The membranes in the adult myocardium that control calcium flux and the contractile system that responds to calcium are present in the fetal heart; however, structures associated with the mechanics of force generation (sarcomere, myofibril), those correlated with controlling calcium flux (sarcoplasmic reticulum and other membrane components including receptors, channels, exchangers, transporters, and pumps), those related to myocardial compliance (extracellular matrix/cytoskeleton), and sympathetic innervation undergo qualitative and quantitative age-related changes. In part, age-related differences in cardiovascular function and responses to calcium and other pharmacologic agents can be attributed to the developmental state of these various components of myocardial anatomy and function.

During fetal and neonatal development, myocytes differentiate markedly and increase in number and size, which correlates with profound changes in mechanical properties and therefore contractility and performance. In the perinatal period, the myocytes complete "terminal differentiation" and lose their capacity to proliferate, as evidenced by their

transition from mono- to binucleation (a final nuclear division without cellular division) [111]. Concurrently, the shape and size of myocytes change, gradually remodeling from a spherical to a more rectangular shape by adulthood. Since shortening typically occurs along the long axis, the adult myocyte (dimensions of the adult vs. neonate myocyte: 150 vs. 40 μm in length; 5 vs. 25 μm in width) generates a more rapid response and a larger increase in amplitude than the neonatal myocyte [112].

Recent studies in both human [113] and animal [111] fetuses have documented that the late gestational exponential cardiac growth secondary to the increase in size and number of myocytes correlates with an increase in both left ventricular volume and active tension per unit of myocardial volume. Of possible importance in the setting of congenital heart disease (e.g., single ventricle associated with pulmonary or aortic atresia), marked differences between the development of the left and right ventricles have been noted, including fewer but larger myocytes in the right ventricle [111].

Subcellular Components: In addition to the increased number of myocytes, age-related changes in subcellular components/ultrastructure, and protein composition also contribute to maturation in excitation–contraction and force development in the myocardium and, therefore, cardiovascular function. Not only does the number of myocytes per cross-sectional area increase, but the organization of the myofibrils also undergo striking age-related changes [112, 114]. In the immature myocardium, myofibrils appear in thin layers, and groups of nuclei and mitochondria congregate chaotically in the center of the cell. In contrast, in the mature myocardium, long parallel rows of myofibrils alternate with rows of mitochondria (and sarcoplasmic reticulum). The chaotic arrangement of mitochondria and myofibrils in the immature myocardium contributes in part to the reduced contractility compared with the adult heart.

In addition to the effects of age-related changes in gross anatomy/morphology, the development of various membranes that control the regulation of calcium flux also exerts substantial effects on the force of myocardial contraction. For example, during gestation, heart rate decreases but diastolic filling and ventricular ejection increase [115]. Similarly, others [116] have defined gestational age-adjusted reference values for a "modified myocardial performance index" as well as contraction, relaxation, and ejection times (human fetuses, 20–38 weeks' gestation), hypothesizing that these indices changed secondary to improved ventricular compliance as the ratio of contractile to noncontractile elements increase and myofilaments grow; the data on performance did not correlate with morphologic development. However, in human fetal cardiac muscle, a change in function correlated directly with changes in ultrastructure. Maturation of the sarcomere and changes in protein isoforms (e.g., β-myosin and troponin I) seemed to underlie the developmental changes in performance [114]. Similarly, changes in contractility during embryonic and fetal development (mouse) were related to both the amount and isoform patterns of sarcomeric proteins, focusing on myosin heavy chains and troponin (actin, myosin light chains, and tropomyosin were not studied) [117].

Both the cell membrane (sarcolemma) and the intracellular sarcoplasmic reticulum modulate the increase in cytosolic calcium that facilitates contraction and undergo developmental changes. In the adult, a small calcium influx via L-type calcium channels stimulates calcium release from the sarcoplasmic reticulum (calcium-induced calcium release [CICR]). CICR depends on an intricate coupling of the L-type calcium channel, the ryanodine receptor (RyR), and T tubules (invaginations of the sarcolemma) [118, 119]. Despite differences among species, CICR has been allocated a secondary role in the generation of a myocardial contraction in the immature myocardium because of limited sarcoplasmic reticulum and underdeveloped T tubules [120, 121]. Instead, contraction relies more on the L-type calcium channels and extracellular calcium (Wu 2016). Recently, attention has focused on a role that links the Na^+–Ca^+ exchanger (NCX) with the RyR to allow an age-defined reverse version of CICR [122, 123]. These studies document that the NCX and NCX-CICR play a significant role in excitation–contraction coupling in early developmental stages. The notable contribution of calcium influx via reverse-mode NCX correlates with the greater expression and activity of NCX in the neonatal heart [122]. An L-type calcium current mediated by CICR plays an increasingly critical role as the myocardium matures, although the details of the molecular mechanisms remain unclear. Finally, in addition to RyR-gated calcium flux, inositol 1,4,5-trisphosphate (IP(3)-gated Ca(2+) release channels also contribute to activating CICR to induce cardiac contraction [124]

Clinically relevant developmental changes are pervasive in the developing myocardium including the sarcoplasmic reticulum, T tubules, and various channels and regulatory proteins. For example, the force generated by the human left ventricle increases substantially between approximately 8 and 20 weeks' gestation [114] but remained less than 50% of the specific force of healthy adult ventricle myofibrils [114]. Relevant to this, the volume of sarcoplasmic reticulum and its ability to pump calcium (uptake, longitudinal sarcoplasmic reticulum; storage and release, junctional sarcoplasmic reticulum) increase in utero and postnatally. Furthermore, the various subtypes of sarcoplasmic reticulum are less differentiated functionally in the immature heart. As a result, immature hearts are more sensitive to calcium channel antagonists [125], and maximal contractility depends to a greater extent on extracellular calcium that does the mature heart [126].

When compared with the adult myocyte, the reduced velocity and magnitude of sarcomere shortening [114] in the immature myocyte in part may be attributed to age-related changes in expression of various isoforms of contractile pro-

teins such as troponins [127]. The troponin complex, which consists of three subunits (structural proteins: troponin C, I, and T) and binds to the thin filament of the myofibril, regulates activation of the interaction of actin and myosin (calcium-dependent) that results in force generation. Both troponin I and T exist in multiple isoforms that are developmentally regulated. For example, an isoform identical to that in slow skeletal muscle (ssTnI) is expressed in embryonic, fetal, and neonatal myocardium [114, 128], whereas the cardiac isoform (cTnI) is expressed predominately in the adult myocardium. Of note, by 9 months of postnatal development, cardiac troponin I is the only detectable isoform.

The myocardial expression of the slow skeletal muscle in terms of the cardiac isoforms of troponin I may be of particular importance in the immature myocardium since this has been correlated with the relative resistance of the immature heart to acidosis [129]. The response of the immature myocardium to sympathetic stimulation is similarly correlated with the expression of slow skeletal troponin I. Cardiac, but not slow skeletal muscle, troponin is phosphorylated in response to β-stimulation, which may correlate with the difference in diastolic function noted in the neonate [130]. This phosphorylation decreases the sensitivity to calcium, facilitating diastolic relaxation.

TnT isoforms vary among species and stages of development. The human cardiac muscle contains four isoforms of TnT (cTnT 1–4); cTnT1 expression peaks in the fetus, whereas only cTnT3 is expressed in the adult. Calcium sensitivity has been correlated with the shift in the expression of the troponin T isoform [127]. The expression of specific isoforms of troponin T has been correlated with the responsiveness of myofilaments to calcium.

Although cardiac troponins are routinely used to evaluate and monitor cardiac injury in children and adults, only recently has their importance in the intensive care nursery been recognized [131]. Troponins are typically bound to the thin filament of the myofibril, but with acute injury to the myocardium, bound troponin is released from damaged tissues, first appearing in blood after 2–4 h and persisting for up to 21 days. The range of normal concentrations of the isoforms of troponin in the neonate has been reported for both cTnT and cTnI. The concentrations of troponins in cord blood samples vary as a function of gender, mode of delivery, and assay. Both cTnT and cTnI increase after asphyxia-associated myocardial injury, although the variability in the responses among studies is notable. As in children and adults, laboratory evidence of injury is often an adjunct to other assessments (e.g., echocardiogram) of cardiac function. For example, asphyxiated neonates have greater concentrations of cTnT than normal-term infants that correlate with echocardiographic evidence of myocardial dysfunction. Nonetheless, in many cases, cardiac output is similar in asphyxiated and non-asphyxiated neonates. The concentrations of troponins are generally increased in preterm infants, although treatment with inotropes correlates with greater cTnT concentrations in both term and preterm neonates. Thus, although troponin concentrations are likely to become an integral segment of evaluating perinatal injury in both preterm and term infants, specific prognostic and therapeutic roles have not been completely defined. Nonetheless, recent reports suggest that significant increases in cord troponin is an excellent and early predictor of the severity of hypoxic–ischemic encephalopathy (HIE) and mortality in term infants [132]. Similarly, measuring brain natriuretic peptide is a reliable test to diagnose significant structural or functional cardiovascular disease but should be considered an adjunctive marker, not a stand-alone test [132, 133].

Myocardial Compliance: Extracellular Matrix/ Cytoskeleton

The cytoskeleton includes the contractile proteins and titan (a large protein that extends over half the span of the sarcomere) as well as microfilaments, intermediate fibers, and microtubules. This intricate complex provides the structural framework for intracellular and extracellular communication that allows the contractile movement of the individual sarcomeres to be translated into effective systolic contraction and diastolic relaxation. That is, the cytoskeleton provides the system for mechanical signaling. Examining the general appearance of the immature sarcomere provides an overview of the dramatic changes in organization that occur during early development. In the immature myocyte, A and I bands are more irregular, M bands are absent, and Z bands vary in width. Several of the proteins and microfilaments, intermediate fibers, and microtubules develop postnatally, which is critical in mediating a range of activities such as cell growth, migration, and adhesion as well as signaling for remodeling in response to the adaptation of the transitional circulation at birth [48]. For example, desmin, a protein that links Z bands of myofibrils, improves the connection of myofibrils with mitochondria facilitating the mechanics of contraction. The expression of various isoforms of collagen (amount and types) that improve the resting load and passive state of the myocardium undergo developmental changes. For example, the type I isoform correlates more tightly with developing rigidity, whereas the type III isoform contributes to elasticity, and the relative proportion of these two correlates with myocardial compliance. As the collagen network becomes progressively more organized with maturation, the population of type III isoform increases, eventually equaling or exceeding that of type I [134]. That is, the ratio of isoforms (I:III) is increased in preterm and term infants, a level that persists until at least age 6 years, but then decreases thereafter to ~0.5 by adulthood [134].

Adrenergic Function

The sympathetic nervous system modulates cell growth and differentiation, as well as the distribution of and sensitivity to calcium. Of note, the increased concentration of α-adrenoreceptors in the early postnatal period may be critical in stimulating left ventricular growth [135]. For example, $\alpha\text{-}_{2A}$ adenoceptors affect growth by stimulating actin organization (cytoskeleton) [136]; $\alpha\text{-}_{1A}$ receptors seem to mediate inotropic activity [137, 138], not hypertrophy. Several studies (mice, rabbits) report a developmental increase (i.e., as gestation advances) in the density of β-adenoceptors [139, 140], but other studies suggest that although the receptors increase with development, "specific activity" decreases [141]. Recently, the expression of β_1-adenoceptors was documented to be reduced in the preterm heart (pig) and unaffected by maternal glucocorticoids [142]. On the other hand, $\alpha\text{-}_{1A}$ receptors (quantity of mRNA) did not differ in preterm compared with term ventricles. Finally, the activity of adenylate cyclase, an important enzyme involved in the intracellular transmission of β-stimulation, increases in parallel with the increase in catecholamine concentrations [141, 481]. Of note, glucocorticoids delivered to the mother to promote in utero lung maturation may play a significant role in adrenergic receptor expression and subsequent neonatal cardiac function [143, 144], but other studies report conflicting data [142].

Although incompletely elucidated, the role of the cardiac opioid system in regulating the myocardial function seems especially relevant to the development of the sympathetic and parasympathetic innervation of the neonatal heart. For example, in one report enhanced expression of δ-opioid receptors paralleled the maturation of parasympathetic, sympathetic, and sensory innervation of the heart, suggesting that the cardiac opioid system may regulate aspects of neonatal heart function [145].

Thus, in general, the increase in the network of adrenergic fibers innervating the myocardium induces widespread development and expression of the various contractile systems (e.g., the expression of the contractile proteins, the efficiency of the calcium channel, expression of the myosin ATPase isoforms). On the other hand, the controversial and variable data about the expression and function of neonatal adrenergic receptors imply that specific inotropic support to maintain cardiovascular stability in the neonate, especially the preterm infant, remains imperfect. In many cases, a trial of a variety of traditional and newer agents constitutes the routine approach to bedside care, especially in the preterm infant.

The Preterm Infant

The typical changes of the transitional circulation are blurred in the setting of the very low birth weight (VLBW, <1500 g) and extremely low birth weight (ELBW, <1000 g) infant. The early postnatal hours of the preterm infant are often considered one of the most unstable periods, often characterized by "low systemic flow" [146]. At less than 30 weeks' gestational age, the ductus arteriosus often fails to close, systemic and pulmonary vascular resistances are high relative to the placental circulation, and often the cardiac output does not increase dramatically in the first 24 or more postnatal hours. Although the Frank–Starling relationship (increasing preload increases stroke volume, up to a point) exists, the immature myocardium renders this population more vulnerable to cardiovascular instability, especially during the transition from fetal to extrauterine life. At the same time, because of the unique physiology of the ELBW infant, assessing or measuring cardiac output and establishing "normal" values for systemic blood pressure and heart rate become complicated; defining hypotension becomes difficult (see below) [147]. Consequently, diagnostic and therapeutic regimens in the intensive care nursery cannot be established based on clear-cut, abundant, evidence-based data.

At any developmental stage, ventricular function is governed by the same factors: preload, afterload, contractility, and heart rate. However, the ability to compensate for perturbations in these factors is limited in the neonate, especially in ELBW infants. In the preterm infant (i.e., in some cases, a mid-gestation fetus), the immature myocardium and the peripheral circulation present significant disadvantages when, at birth, the low-resistance placenta is abruptly replaced with the high-resistance pulmonary and systemic vascular beds, and interventions such as positive pressure ventilation and inotropic support are introduced. The preterm infant may also be dramatically sensitive to changes in heart rate. Marked variability in the quantity of blood flowing across the foramen ovale and ductus arteriosus adds to the complexity of monitoring the cardiovascular function of the preterm infant.

The relationship between blood pressure, cardiac output, and systemic vascular resistance is constant throughout life: BP = CO X SVR. That is, pressure and flow are not equal but are related via resistance (SVR). Thus, flow to an organ may increase, decrease, or remain constant over a wide range of blood pressures depending on changes in resistance. Although the normal ranges for blood pressure correlate with gestational age [148, 149], the definition of hypotension remains elusive [150]. Because a mean arterial pressure <30 mmHg for more than 1 h (measured on the first day of life, beginning at 5 h) has been associated with intracranial lesions [151] and/or adverse neurodevelopmental outcome [152] or reduced cerebral blood flow (CBF) [153], many set a breakpoint for hypotension at 30 mmHg in preterm infants. However, others hold that the normal mean arterial blood pressure is <30 mmHg in the most preterm infants during the first 3 postnatal days (Fig. 2.6) [154]. And others suggest that a mean blood pressure that is less than the gestational age correlates with the 10th percentile for blood pressure

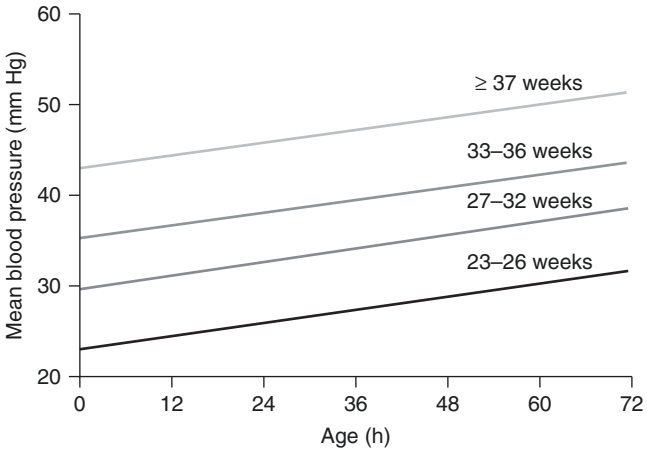

Fig. 2.6 Mean blood pressure in neonates predicted lower limit (initial 72 h of life) (from Nuntnarumit et al. [154])

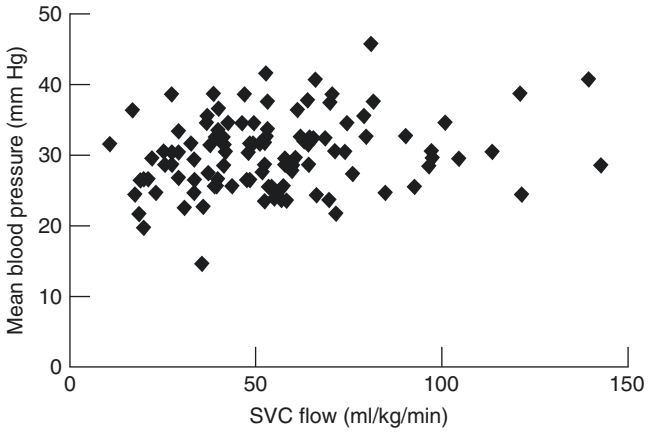

Fig. 2.7 Ultrasound-measured flow in the superior vena cava has been validated as an estimate of CBF. Note the lack of correlation of SVC flow with simultaneously measured mean arterial blood flow (from Kluckow and Evans [172])

[155, 156], and this constitutes a definition of hypotension. A recent study in ELBW infants noted that arterial blood pressure reached a nadir during the initial 5 h after birth, increasing steadily afterward at a rate of 0.2 mmHg/h [157].

Although studies have reported an association between hypotension and intraventricular hemorrhage [158, 159], a clear cause-and-effect relationship remains controversial (see Autoregulation). That is, aggressive treatment of "hypotension" has not been shown in prospective studies to affect specific indices of cardiac function [160], morbidity or mortality [147], or long-term outcome [161–164]. And, unfortunately, identifying links between a specific inotropic agent, change in CBF, and outcome remains at best an estimate. No study "has shown any improvement in any meaningful clinical outcome, short or long term, in response to a specific inotrope" [150, 165].

Thus, the variability in "normal" for blood pressure and heart rate among infants of the same gestational and/or postnatal age creates a dilemma in the setting of clinical care, especially in the commonly unstable setting of the operating room. Furthermore, without access to reliable measures of perfusion to critical organs (i.e., the brain), devising precise guidelines for treating "hypotension" in the neonate is virtually impossible.

Several investigators [150, 166, 167] have proposed a novel approach to monitor CBF in the setting of the transitional circulation of the preterm infant, especially in the first few postnatal days. Recognizing that neither blood pressure [166, 167] nor capillary refill time [168] reliably correlate with left ventricular output in the preterm infant, the flow in the superior vena cava has been measured to estimate systemic blood flow to the brain (and upper body). Measuring blood flow of the superior vena cava eliminates the need to consider the influence of shunting via either the ductus arteriosus or the foramen ovale on the accuracy of this measurement [169]. In these studies, mean arterial pressure correlated poorly with superior vena cava flow (Fig. 2.7). Similarly, others noted that during the first 48 h of life, blood pressure did not correlate with the volume of blood flow in the descending aorta, superior vena cava, or left or right ventricle [167]. If a relationship between blood pressure and blood flow in the superior vena cava existed at some time points, it would most accurately be labeled as being "inverse, as reported in earlier studies" [170]. Of interest, neither dopamine nor dobutamine increased contractility when introduced in response to reduced superior vena cava blood flow [171].

Measuring superior vena cava flow (and other flows) may improve the accuracy of ensuring adequate oxygen and nutrient delivery, especially to the brain, and monitoring the effectiveness of therapy. For example, superior vena cava flow has been correlated with both the incidence of periventricular hemorrhage and neurodevelopmental outcomes [152, 172]. This method of "functional echocardiography" is evolving as a more common bedside monitor [156, 173–175]. When combined with algorithms derived from near-infrared spectroscopy (NIRS), "optimal blood pressure" may eventually guide clinical therapy that reliably preserves CBF (see Autoregulation).

However, at present, given our inability to easily and accurately measure the cardiac output and organ-specific blood flow (e.g., CBF) in the neonate (Fig. 2.7), systemic blood pressure and heart rate, bedside echocardiography, and metabolic indices including blood gases/lactate/electrolytes and trends in clinical status remain the primary parameters to track cardiovascular homeostasis in the neonate, especially the ELBW infant [156]. Coupled with the intense variability and unpredictability of blood pressure and response to vasopressors, the physiology of the neonate requires man-

aging patients individually with meticulous reassessment. Even investigators who reported the relevance of superior vena cava flow remain focused on rational clinical care based on commonly available cardiovascular indices [165], with repeated reassessment to guide and modify management. As always, a parameter such as blood pressure must be interpreted within the wider context of other clinical and diagnostic data. For example, even if superior vena cava flow was measured, these data might be correlated with MRI and clinical status to fine-tune therapies.

Clinical Significance and Summary

The neonate has the highest cardiac output per body weight of all age groups (~300 cc/kg/min). This increased resting cardiac output limits the neonate's ability to respond to an increased oxygen demand or to adapt to wide variations in preload or afterload. That is, the neonate cannot readily compensate for inadequate blood flow if the preload becomes inadequate or if afterload increases, or if heart rate, or contractility wanes. For example, the non-distensible heart has limited capacity to increase stroke volume to augment cardiac output in response to increasing preload [176, 177]. Although volume loading in the immature ventricle increases cardiac output, the effect is attenuated compared with the response at older ages. Similarly, the immature myocardium poorly tolerates increases in afterload compared with that at older ages. The increased content of collagen and high ratio of types I:III collagen may account for the relative noncompliance of the neonatal heart. These factors are all magnified in the setting of the ELBW infant where blood flow across the foramen ovale and ductus arteriosus varies markedly over short periods. Finally, since the normal heart rate in the neonate is high, increasing the heart rate may not further increase the cardiac output, but decreasing the heart rate may dramatically decrease the cardiac output. Some propose that the resting myocardium in the neonate exists at a greater level of "β-adrenergic tone" than does the child and adult. As this β-adrenergic tone wanes over the first weeks to months after birth, adrenergic stimulation may elicit a greater increase in cardiac performance [178].

The fetus (i.e., ELBW infant) and neonate may have impaired ventricular function secondary to a decreased number of myofibrils, decreased sympathetic innervation, decreased β-adrenoceptor concentration, immaturity of the sarcoplasmic reticulum structurally and functionally maturation-specific mechanisms for calcium uptake, release and storage, and specific spectra of expression of various isoforms of contractile/noncontractile proteins, channels, exchangers, and enzymes. Over the first months of life, myocardial contractility gradually increases, which maintains cardiac output over wider ranges of preload and afterload. Similarly, the increase in contractile proteins and the shift in expression to various isoforms, the development of sarcoplasmic reticulum and T tubules, and adrenergic innervation all contribute to complex changes in force development, calcium recruitment, and transport that prime the myocardium for a more powerful response to stress and increased oxygen demands.

Central Nervous System Function

Discussing the central nervous system after the cardiovascular function is intentional since the physiologic vulnerability of the immature brain is inextricably linked to age-related hemodynamic function. Circulatory immaturity undoubtedly plays a fundamental role in perinatal brain injury. Hemodynamic instability is common in the neonatal period (especially in the preterm infant) and has been implicated in ischemic and hemorrhagic brain injury in both term and preterm infants. Unfortunately, cerebrovascular injury has been linked to lifelong dysfunction including motor disorders, learning/developmental delays, seizures, and secondary complications (e.g., from chronic lung disease secondary to recurrent aspiration pneumonia). Minimizing or preventing neurologic complications from perinatal injury requires a complete understanding of the cellular and molecular mechanisms of the responses of the developing brain to asphyxia, hypoxia, and/or inflammation. To date, such mechanisms have not been definitively mapped, and the extent and nature of the initial injury does not invariably predict long-term outcomes.

The general pattern of injury to the developing brain involves an initial insult from hypoxia, inflammation, and/or ischemia followed by secondary damage from reperfusion that results in excitotoxicity and release of a host of cytokines [179]. Recently, Volpe introduced the concept of "panencephalopathy" [180] and "encephalopathy of prematurity" [181–183] to emphasize that the initial white and gray matter injury incurred by the preterm infant is not simply a simple loss of tissue. That is, injury to the immature brain significantly impairs subsequent development by disrupting "connectivity." Volpe emphasizes that "neonatal brain injury and its subsequent clinical and anatomic consequences must be viewed as an amalgam of destructive and developmental disturbances." Kinney asserted that the term "encephalopathy of prematurity" implies that "the constellation of cognitive, motor and emotional impairment in long-term survivors of prematurity reflects the particular patterns of white and

gray matter damage in combination with arrested developmental programs—patterns that depend upon the severity, timing, and chronicity of the injury as well as individual confounding factors" [184].

Normal Development of the Central Nervous System

The two primary structures of embryogenesis of the brain that develop early in gestation are the neural tube (future brain and spinal cord) by 3–4 weeks and the prosencephalon (future forebrain) by 2–3 months [185]. Early neural tube anomalies are dramatic and often fatal: anencephaly, craniorachischisis totalis, myeloschisis, and encephalocele. Similarly, severe prosencephalic anomalies (holoprosencephalies) are often fatal, especially when associated with chromosomal abnormalities (e.g., trisomy 13–15, trisomy/ring/deletion 18). kpo6

As a less severe form of abnormal neural tube closure, lesions of spina bifida (incidence 3–7 per 10,000 births) are clinically important because affected infants frequently survive and have lifelong problems. The four primary types of spina bifida are categorized according to the severity of the defect [185]. In spina bifida occulta, the divided vertebral arch, the spinal cord, and the meninges are covered with skin. Hair often protrudes from the skin overlying the defect, forming a sacral dimple. In spina bifida cystica, neural tissue and its coverings protrude through the incompletely formed vertebral arch as a cystic-like structure. In meningocele, the neural tube lies in its normal position, but the meninges protrude through the defect; skin usually covers this lesion. In the fourth type, the myelomeningocele, both the spinal cord and the meninges protrude, often without skin. These lesions can occur at any level of the spine. Hydrocephalus, which commonly accompanies myelomeningocele (in 60% of those with occipital, cervical, thoracic, or sacral lesions and in about 90% of those with thoracolumbar, lumbar, and/or lumbosacral lesions) [186], is often not evident before the meningomyelocele is closed because cerebrospinal fluid leaks through the open lesion and decompresses the ventricles.

Arnold–Chiari malformation, an abnormality of the hindbrain, occurs in most patients with myelomeningocele. The medulla oblongata is flattened and elongated and, along with the fourth ventricle, protrudes into the spinal canal through the foramen magnum. The downward position of the medulla elongates the lower pons and upper medulla and may compress brain stem nuclei and cranial nerves. If the cerebellar tonsils are displaced through the foramen magnum, aqueductal stenosis and associated hydrocephalus can develop. Severe anomalies may cause apnea, vocal cord paralysis, and/or central and obstructive ventilatory disturbances and require early correction [187]. Of significance, as many as 20% of infants with myelomeningocele have sleep-disordered breathing [188].

Agenesis of the corpus callosum and septum pellucidum is often associated with abnormal neuronal migration and significant clinical abnormalities. Agenesis of the corpus callosum is usually associated with a syndrome (e.g., Aicardi or Andermann syndrome) or a chromosomal [11, 14, 16, 18, 21] abnormality. As many as 80% of children without a corpus callosum have other brain anomalies, as well as non-CNS malformations [189, 190]. Partial agenesis of the brain probably occurs later in development and is associated with clinical syndromes with migrational and structural disorders. Agenesis of the septum pellucidum is never an isolated lesion, often occurring in conjunction with optic nerve hypoplasia (septo-optic dysplasia).

During the third trimester, cortical gray and white matter volumes increase four- to fivefold [182, 183], secondary to growth and differentiation of dendrites and axons, the proliferation of glia, synaptogenesis, and myelination (Fig. 2.8) [191]. The proliferation in the cerebellum is even more rapid than the cerebral cortex and is characterized by intense migration of various populations of cells (Fig. 2.9) [192–194]. In parallel with the intense growth of the parenchyma, the vascular network of the late gestation brain also develops rapidly. The long and short penetrators lengthen and arborize, decreasing border/end zone blood flow.

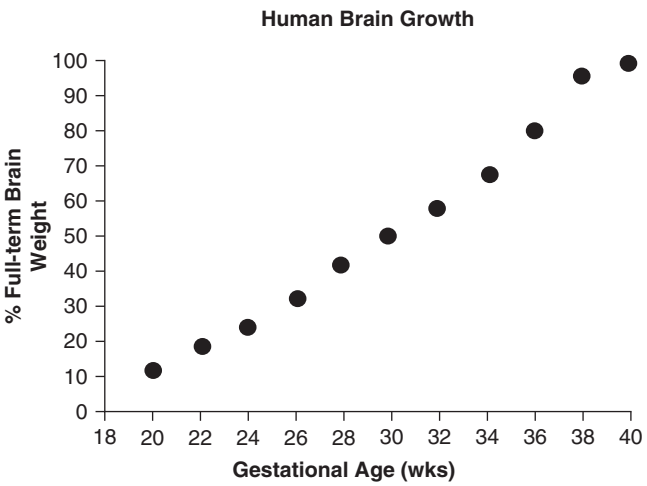

Fig. 2.8 Growth of the human brain over the second half of gestation as a function of % of the weight for the full-term infant. The 34-week gestation brain is only 65% of its weight at term (from Kinney [191])

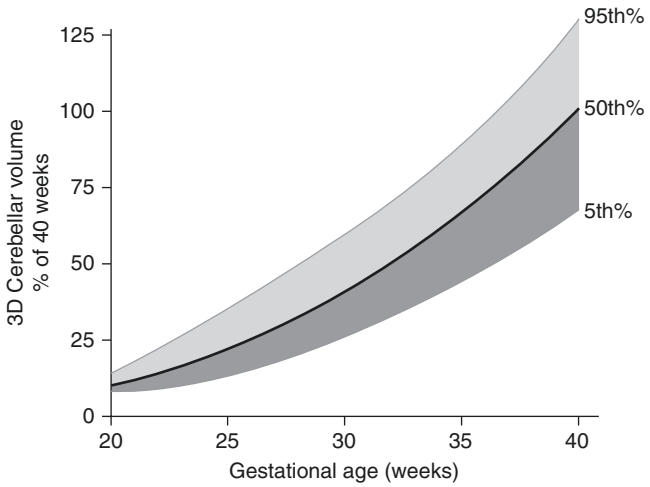

Fig. 2.9 Growth of the human cerebellum (5th, 50th, 95th percentile) during the last half of gestation as a function of % of the volume for the full-term infant. The 34-week gestation brain is only 65% of its volume at term (from Volpe [195])

Age-Related Patterns of Injury

In addition to the overall intense growth of the brain in late gestation, specific transient cell types define the unique susceptibility of the developing brain to ischemia, inflammation, excitotoxicity, and free radical injury. That is, various populations of cells are critical in forming pathways in the central nervous system and, at the same time, are exquisitely sensitive to injury. This selective vulnerability of specific populations of cells at different developmental stages (24–28 weeks vs. 28–32 weeks vs. 32–37 weeks vs. term) leads to predictable patterns of injury and associated pathology [196]. Thus, the specific characteristics of an insult and tissue combine with gestational age resulting in unique cellular vulnerability that defines pathology and associated clinical outcome. Three examples have received prominent attention by experts in neonatal neuropathology (see Vulnerable Cell Populations).

In general, the preterm infant, especially VLBW infants, is considered to be the infant most vulnerable to white matter injury, whereas the term infant is most vulnerable to injury in the deep gray nuclei (e.g., basal ganglia and thalamus). However, advanced MRI (e.g., high-resolution MRI, spectroscopic imaging, diffusion tensor imaging) has expanded our understanding of brain development leading to the "blurring" of this "gray-white" dichotomy of the response to injury in the term versus preterm infant [197]. For example, periventricular white matter in preterm infants is selectively vulnerable to ischemia during hypotension [198]. But, increasingly, white matter injury has been recognized in term infants, and gray matter injury has been identified in preterm infants [180, 199–201]. Finally, the cerebellum seems uniquely vulnerable to injury in the preterm infant [199, 201, 202]. Furthermore, the detailed anatomy of injury identified via MRI may be combined with the known selective vulnerability of various cell populations to estimate, first, the patterns of defective "connectivity" in brain development that develop after the injury and, second, to correlate these patterns with the clinical outcome identified during long-term follow-up [199, 200].

Patterns of injury common to preterm and term infants involve various excitatory mediators. For example, although glutamate plays a critical role in the proliferation, differentiation, and migration of developing cells, excessive release of this molecule in the setting of a hypoxic–ischemic injury contributes to a state of "excitotoxicity" that is associated with cell death. When glutamate receptors (*N*-methyl-d-aspartic acid [NMDA], alpha-3-amino-hydroxy-5methyl-4-isoxazole propionic acid [AMPA], kainate) are excessively stimulated (especially certain subtypes), intracellular calcium accumulates and activates caspase-3, which leads to abnormal apoptosis. The NMDA receptor predominantly mediates this activity, and one subunit (NR2B) that predominates early in gestation mediates slower deactivation, resulting in prolonged action compared with other subunits [203]. In addition to excitotoxicity, oxidative stress seems fundamental to the widespread injury to the brain of the neonate, especially the VLBW infant. When the production of toxic free radicals exceeds the availability of antioxidants to neutralize the excessive level, the imbalance leads to disruption of fundamental cellular structures (e.g., DNA, lipids, and proteins). Preterm infants are especially prone to oxidative stress secondary to exposure to events that predispose to this condition (i.e., hyperoxia, hypoxia, ischemia/reperfusion, infection/inflammation, blood transfusion/iron load) in the presence of limited antioxidant capacity (e.g., vitamins A, C, and E, catalase, glutathione peroxidase, Mg and Cu superoxide dismutase) [203–205]. Although a specific mechanism for injury is elusive, painful and stressful procedures encountered during neonatal intensive care have been associated with disturbances in brain growth and maturation [201, 206]. Most complications of prematurity (e.g., retinopathy of prematurity, bronchopulmonary dysplasia, necrotizing enterocolitis, intraventricular hemorrhage, periventricular leukomalacia, diffuse white matter injury, punctate white matter lesions) have been linked to oxidative stress [207]. Consistent with this, Saugstad suggested the term "the oxygen radical disease of neonatology" [208]. On the other hand, while harmful in excess, low or moderate concentrations of reactive oxygen species and reactive nitrogen species are critical factors in various processes such as maturation of cellular structures and host defenses.

Of interest, areas of the brain expressing NMDA receptors also express neuronal (nNOS) and inducible nitric oxide synthase (iNOS) [209]. While endothelial nitric oxide (eNOS)

mediates cerebral vasodilatation, excessive nitric oxide mediated by iNOS in response to hypoxia–ischemia generates reactive nitrogen species (free radicals). The excess oxygen and nitrogen free radicals generated in response to hypoxia–ischemia or to free iron (Fenton reaction generates the hydroxyl radical when hydrogen peroxide encounters free iron) [210, 211] associated with hemorrhage deplete endogenous antioxidant systems, damaging cell membranes and resulting in cell death. Oxidative stress seems to enhance excitotoxicity via regulatory effects on glutamate receptors [212].

Therapy with antioxidants (caffeine, an adenosine inhibitor; melatonin, free radical scavenger, pro-myelination function; recombinant human insulin-growth factor 1, stimulates growth and differentiation) has been proposed, but clinical studies remain in early stages [204, 208]. Also, erythropoietin has been shown to provide neuroregeneration in the setting of hyperoxia-induced brain injury (rat), implying a possible therapeutic role in the preterm infant [213].

Vulnerable Cell Populations: The Preterm Infant

Two unique cell types (subplate neurons and pre-oligodendrocytes) with marked sensitivity to hypoxia–ischemia populate the white matter of mid-gestation fetuses and express glutamate receptors. The subplate neurons located in the subcortical white matter first appear at ~10 weeks' gestation and peak in number between 24 and 32 weeks [203, 214], when the subplate zone is 4–5 times thicker than the cortical plate. The subplate serves as a waiting zone for cells and thalamocortical axons until their final ultimate location in the cortex is defined [215]. That is, postmitotic cortical neurons migrate through the subplate along "radial glial guides" on their way to the cortical plate. As noted by Kostović, "the subplate becomes the thickest and most voluminous transient compartment of the human fetal cerebral wall between 15 and 35 weeks gestation and represents the major site of synaptogenesis and neuronal maturation and differentiation. Before 24 weeks, the subplate is the major site of synaptogenesis in the fetal brain. Between 28 and 34 weeks' gestation, this region remains at the peak of its development because of continuous growth and relocation of massive corticocortical pathways; this period is also characterized by extensive growth of fetal white matter, further formation of cortical convolutions, and exponentially increasing synaptogenesis" [216]. Damage to the subplate in the preterm infant during the "waiting period" when thalamocortical fibers are rapidly accumulating (~22 weeks) and during relocation into the cortical plate (~24–28 weeks) may lead to abnormal cerebral development. That is, the subplate functions as a "waiting compartment" for cortico-cortical afferents until birth and even as a "mini-waiting compartment" after birth [216]. Although the subplate diminishes after 34 weeks' gestation and a distinct subplate zone is not distinguishable 6 months after birth [217], subplate neurons continue to develop postnatally, populate the adult gyral white matter [218], and are referred to as "interstitial white matter cells" [217, 219]. As one expert noted, "transient populations of cortical neurons generate such great interest because they are the link between developing and mature cortical circuits"; subplate neurons have been investigated as links to psychiatric disorders and brain abnormalities, including epilepsy, autism, bipolar disorder, and schizophrenia and various developmental abnormalities secondary to migrational disorders [217, 220]. Finally, hypoxic–ischemic injury to the subplate zone either in utero or in preterm infants may predispose to these disorders as well as cognitive problems in later life. For example, injury to a vulnerable subpopulation of neurons (granular neurons) in the white matter and subplate region of humans in the setting of periventricular leukomalacia supports an association between insults at certain critical phases of development and later neurodevelopmental and cognitive dysfunction [221].

In summary, by expressing various neurotransmitters and growth factors, this subplate zone orchestrates the migration of cells from the germinal neuroepithelium to distant sites (e.g., corpus callosum, basal ganglia, thalamus) and initiates formation of synapses [217, 220]. These neurons have abundant receptors for excitatory amino acids (e.g., glutamate) that are critical modulators for normal development, but hypoxia–ischemia may stimulate excessive release of these modulators, excitotoxicity, and white matter injury. In vitro studies have documented the relative sensitivity of subplate neurons to glutamate compared with other cortical cells [222]. Damage to the subplate may disrupt axon development in vital sites such as thalamocortical areas, impeding critical innervation and interaction, interrupting feedback between the cortex and thalamus, and leading to long-term functional consequences. Interfering with the connectivity among various distant structures during a period of critical brain development has been postulated to correlate with deficits identified in the ex-premature in the specific areas of behavior, cognition, and other complicated higher cortical functions (e.g., executive function) [193, 223–226]. Thus, the subplate neurons are a transient cell population that mediates essential thalamocortical development.

Before myelination and during the time of peak vulnerability to white matter injury (23–32 weeks) (see "Cerebral White Matter Injury"), the late oligodendrocyte progenitors (pre-oligodendrocytes) are the predominant cells that populate the subcortical white matter. While mature oligodendrocytes are relatively resistant, pre-oligodendrocytes are especially susceptible to injury from oxidative and excitotoxic stress and, when injured, fail to reach full maturation, resulting in diffuse hypomyelination and axonal disruption. Thus, injury

to progenitors inhibits their maturation, allowing the persistence of a population of cells that exhibit excitotoxicity as well as fail to generate mature oligodendrocytes that are capable of myelination [201, 227].

Finally, microglia are concentrated in the cortical white matter during the third trimester but decline rapidly after 37 weeks of gestation [228]. Recently described as "'gatekeepers' of a healthy brain microenvironment and cell–cell communications under physiological conditions" [228], microglia exert a broad range of functions during normal development (immune surveillance, vasculogenesis, neurogenesis, myelination, network connectivity). To fulfill such varied roles, these cells display a range of morphological and ultrastructural phenotypes. On the other hand, abnormal activation of these cells secondary to infection/inflammation precipitates the release of cytokine and glutamate, producing reactive oxygen and nitrogen species [201, 211, 229, 230]. Because stimulation of microglia isolated from embryonic and neonatal brains is associated with a greater release of cytokines [229], preterm infants may be complete increased risk for injury secondary to microglia-mediated cytotoxic effects during infection/inflammation. Of note, microglial activation and release of excess cytokines after immune stimulation in the developing brain may not only induce inflammation but also directly affect neurotransmission [228]. Such injury and/or immune stimuli have been reported to stimulate innate immunity via Toll-like receptors (TLRs). Although mediating TLR2 expression during normal postnatal brain development and pathologic conditions, microglia mediate excessive release of proinflammatory cytokines that may be associated with long-term pathology, such as white and gray matter injury [231]. These cells also play a role in the response to ischemic insults associated with stroke [230]. Currently, the complex role of microglia both in normal development and in the emergence of neurologic outcomes after perinatal insults has yet to be fully elucidated.

Thus, after the neural tube and the prosencephalon are established, the central nervous system primarily develops by proliferation and migration. Neurons proliferate from ventricular and subventricular regions at every level of the developing nervous system. From the second to the fourth month of gestation, most proliferating cells are neurons. From the fifth month of gestation to adulthood, glia are primarily proliferating. Interruption of migration (e.g., from the subplate), abnormal activation (e.g., microglia), and/or failure of proliferation/maturation (e.g., pre-oligodendrocytes) are key factors underlying the pathophysiology of injury to the immature brain.

The risk of white matter injury and the associated neurodevelopmental abnormalities increase with systemic illness such as chronic lung disease [232] and necrotizing enterocolitis [233]. Moreover, the critical care of neonates is complex, including pharmacologic therapy, ventilatory support, infections, seizures, and hemodynamic instability, all interacting to produce the outcome.

Vulnerable Cell Populations: The Term Infant

The term infant experiences hypoxia–ischemia from several clinical sources (placental injury [e.g., abruption, infarct], birth trauma, umbilical cord prolapse/compression) that are distinct from those that commonly injure the preterm infant (e.g., infection/inflammation). In general, hypoxic–ischemic insults in the term infant primarily target the deep gray nuclei, especially the basal ganglia. As in the preterm infant, the selective vulnerability is linked to overexpression of certain glutamate receptors (especially NMDA) and various subunits (e.g., NR2B > NR2A). In the basal ganglia, these receptors coexist with an abundant population of neurons that express nNOS, thus creating a site of increased susceptibility to injury. Additionally, free radicals generated from hypoxia–ischemia as well as from reactions with free iron (the Fenton reaction produces the hydroxyl radical when hydrogen peroxide reacts with free iron) generated after hemorrhage may lead to oxidative damage [234].

Contrary to the traditional belief that injury recognized at birth is often associated with chronic in utero events (e.g., infection/inflammation), most neonatal encephalopathy is secondary to insults at or near birth [235–237] and evolves over the first few weeks (or months) of postnatal life. Since such injury is relatively acute but does evolve, neuroprotective therapy may be critically relevant for improving long-term outcomes. In 2010, the International Liaison Committee on Resuscitation (ILCOR) published guidelines that term infants with signs of moderate or severe perinatal asphyxia should receive therapeutic hypothermia [109]. All western countries now have therapeutic hypothermia as a "standard of care" after moderate and severe perinatal asphyxia [238–240]. Currently, servo-controlled whole-body cooling (rather than head cooling) is preferred to provide stable temperatures, while less labor-intensive to apply. Cooling should start within 6 h of birth, and core temperature is maintained at 33.5°C for 72 h (rectal temperature), followed by rewarming at a rate of 0.5°C/h [238]. Cooling at a lower temperature and/or for more prolonged periods has not been proven beneficial. Hypothermia has been feasible in late preterm infants (gestational age 34–36 weeks), but caution is critical in the setting of sepsis or bleeding.

The significant physiologic effects of cooling demand that clinical experts adhere to strict guidelines and monitoring protocols during therapeutic hypothermia. For example, as expected with decreasing metabolic rate, therapeutic hypothermia (decreasing core temperature to a few degrees) reduces heart rate and cardiac output (e.g., 7% decrease per °C below 37°C). Of note, the unique physiology of calcium

metabolism in the neonatal heart must be considered (see Myocardial Development, Subcellular Components) when interpreting measurements such as blood pressure and cardiac output. Similarly, the production of carbon dioxide decreases ~3–4% per °C, predisposing to hyperventilation in the setting of mechanical ventilatory support (alkalosis may decrease CBF and predispose to seizures). Although these changes are predictable, and even "physiologic," hypothermia also blunts the response to inotropic agents and exaggerates α- compared to β-effects. At the same time, vasoconstriction increases hydrostatic pressure, leading to extravasation of intravascular fluid, possibly decreasing venous return. Finally, diverse effects on coagulation and leukocyte function may predispose to bleeding and infection [241]. At the same time, the multisystem derangements associated with asphyxia (i.e., myocardial depression, pulmonary insults [e.g., meconium aspiration, hemorrhage, pulmonary hypertension], renal and hepatic dysfunction [e.g., drug metabolism], metabolic instability [e.g., hypoglycemia]) add to the complexity of supportive care during therapeutic hypothermia [242, 243].

Despite evidence for its effectiveness, hypothermia yields only modest benefits and is unlikely to be a panacea for preventing long-term complications associated with neonatal encephalopathy. The results of the TOBY (Total Body Hypothermia for Neonatal Encephalopathy) trial reported the following (cooled vs. not cooled): IQ >85–77% versus 63% ($P = 0.05$); cerebral palsy, 21% versus 36% ($P = 0.03$); and without neurologic abnormalities, 45% versus 28% (RR 1.60) [244]. Similarly, a Cochrane review of therapeutic hypothermia in neonates with HIE concluded that although beneficial (number needed to benefit 11 and 8, respectively), the effect on mortality or major disability was small, with a reduction from 61% to 46% [240]. At the same time, the US National Institute of Child Health and Human Development (NICHD) study reported that the primary outcome of death or an IQ <70, which had been significantly less at 18 to 22 months of age in those treated (47% vs. 62%), no longer differed significantly at 6–7 years of age. Of note, at follow-up, the incidence of moderate or severe disability (35% vs. 38%) was similar between the two groups [245].

Thus, with significant risks and imperfect progress on improving outcomes, rather than relying on a single modality such as therapeutic hypothermia, many suggest that a multipronged approach to perinatal neuroprotection/rescue will be essential to improving outcomes [210]. That is, after moderate to severe HIE, ~50% of neonates will die or incur long-term developmental problems. Various strategies have been reported, including erythropoietin (EPO), melatonin, N-acetyl cysteine, inhaled xenon or argon, allopurinol, and magnesium [242, 246, 247]. Of these, EPO has achieved major attention, especially as an adjunct to therapeutic hypothermia.

Although widely recognized as a hematopoietic growth factor, EPO's broad effects as antiapoptotic, antioxidative, and anti-inflammatory led to proposals for a role as a neuroprotective agent in the setting of neonatal HIE [247]. Of note, the increased permeability of the blood–brain barrier in the context of HIE allows this factor to gain access to the central nervous system, compared with limited entry into this protected environment during normal physiology. Larger doses than those used to treat anemia (250 μ/kg) have been evaluated in multiple clinical trials (e.g., often 500–1000 μ/kg or greater) for a variety of total doses. In the setting of HIE, EPO induces a variety of mechanisms associated with neuroprotection (e.g., increased expression of EPO receptors in the central nervous system, increasing production of nitric oxide, inhibited release and increased uptake of glutamate, inactivation of caspase enzymes, upregulation of enzymes that scavenge oxygen radicals, downregulation of proinflammatory cytokines, activation of vascular endothelial growth factor, etc.) [247]. Repeatedly, infants exposed to EPO (alone or in addition to therapeutic hypothermia) had improved neurodevelopmental outcome (usually evaluated at 12–24 months' postnatal age), as measured by reduced death/disability, decreased risk for cerebral palsy, reduced incidence of "breakthrough" seizures/reduced number of infants treated with anticonvulsants, decreased incidence of abnormalities/injury on MRI [247]. Nonetheless, published studies have been limited in size and scope, so that EPO has not yet been adopted at a routine clinical therapy for HIE; robust data attest to safety. Recently, experts have reported the effectiveness of EPO as a prophylactic neuroprotective agent in very low birth weight infants [248]. Ongoing larger phase III clinical trials aim to establish the efficacy of this agent for neonatal HIE, both in term and preterm infants.

Magnesium exerts diverse regulatory actions on neurons and at neuromuscular junctions, but effects on the NMDA receptor defines its proposed role in the setting of neuroprotection [249]. Although the mechanism for inhibiting neuroexcitation has not been established and data are controversial, studies repeatedly explore the role of magnesium in interfering with the rapid influx of calcium that accompanies hypoxic–ischemic insults and that initiates a secondary cascade of injury. Furthermore, magnesium has been allocated anti-inflammatory roles in various pathways (e.g., nuclear factor-κB). Although a recent meta-analysis concluded that antenatal magnesium reduced the risk for cerebral palsy and other motor dysfunction [250], the outcome at school age failed to confirm benefits in motor or cognitive performance, or in behavior [251]. Also, recent reports [252], including a Cochrane meta-analysis concluded: "there is currently insufficient evidence to assess the efficacy and safety of magnesium sulfate when administered to women for neuroprotection of the term fetus" [253]. Similar results were noted in other studies. Despite

these disappointing results, clinical guidelines recommend prenatal magnesium as a neuroprotective agent, focusing on decreasing the incidence of cerebral palsy at early follow-up [249, 254]. Of note, the incidence of cerebellar hemorrhage was reduced among very low birth weight infants exposed to prenatal magnesium [255].

Xenon, a gas that crosses the placenta and the blood–brain barrier, is a candidate agent for neuroprotection by binding to N-methyl-D-aspartate (NMDA) glutamate receptors to inhibit apoptosis in the setting of neuroexcitation encountered with HIE. Although preliminary results from the TOBY-Xe Trial are encouraging [256], the clinical relevance of this agent has not been established. Similar to xenon, preliminary data for melatonin imply a role for neuroprotection. As an endogenous "neurohormone," melatonin imparts antioxidant effects by scavenging free radicals, stimulating various antioxidative enzymes (e.g., glutathione reductase, superoxide dismutase), and inducing activities of calcium-binding proteins [246]. Recently, a limited trial in newborns with HIE noted decreased seizures and white matter abnormalities on MRI, with improved survival without developmental abnormalities (at 6 months) [257]. From the perspective of low risk and the option for both pre- and postnatal delivery, melatonin offers notable advantages for neuroprotection. Other agents (e.g., N-acetylcysteine, allopurinol, biotin) and therapies (stem cells) have gained attention and are under ongoing evaluation [246, 258].

Advanced MRI techniques have identified two primary patterns of injury in the term infant [182, 197, 234]. First, a watershed pattern involves the vascular border/end zones of the white matter that may extend into the cortical gray matter after a severe insult. In general, watershed lesions are more often associated with cognitive than motor disorders. Second, the basal nuclei (basal ganglia/thalamus) pattern involves the deep gray nuclei that may extend throughout the cortex after a severe insult. That is, this pattern often includes diffuse cortical injury. At presentation, these neonates have had more severe clinical abnormalities including intensive resuscitation, severe encephalopathy, and seizures. In general, these lesions are typically associated with more severe cognitive and motor disabilities than in the watershed pattern. However, even when one pattern predominates, the damage is common in the other domain [236]. Thus, the spectrum of deficits on follow-up correlates with the pattern of injury on MRI, rather than simply the severity of the lesion.

Congenital Heart Disease

Two decades ago, the dramatic impact of complex congenital heart disease on neurodevelopment was reported. That is, 50% of neonates with congenital heart disease have microcephaly and neurologic deficits that correlate with long-term neurodevelopmental abnormalities [259], including behavioral, cognitive, social/attention, and motor disorders. Although a broad range of factors (e.g., genetic, environmental, in utero insults, pre- and postoperative events) have been associated with these findings recently, the focus has shifted from documenting brain injuries associated with surgery to analyzing antenatal and preoperative factors governing altered brain maturation in congenital heart disease, especially complex cyanotic lesions [260, 261]. A recent comprehensive review of the main findings on *prenatal* MRI associated with various congenital heart lesions (aortopulmonary transposition, hypoplastic heart disease, tetralogy of Fallot, single ventricle) noted that the abnormalities reflected delayed development of the brain (e.g., ventriculomegaly, extra-axial CSF spaces, lower brain volumes). Furthermore, markers of cerebral metabolism and measurements of microstructure also reflected developmental delay. Of note, *fetuses* with lesions associated with impaired oxygen delivery to the brain (hypoplastic left heart syndrome, critical aortic stenosis, interrupted aortic arch, and aortopulmonary transposition) had more dramatic evidence of delay in brain maturation compared with the fetus with sufficient CBF. In addition to evidence for delayed brain maturation, the most common lesions included punctate white matter injury, periventricular leukomalacia, and stroke [262]. Many studies using a variety of tools (e.g., NIRS, cerebral oximetry, EEG) have documented abnormal cerebral oxygenation in complex congenital heart disease, but the correlation with neurodevelopmental outcomes is inconsistent [260]. Thus, in the setting of complex congenital heart disease, the concept that hypoxic–ischemic injury and dysmaturation in utero coupled with a high risk of acquired brain injury postnatally combine to increase the risk for short- and long-term adverse neurologic outcomes [263].

Similar to fetal MRIs, *preoperative postnatal MRI* in neonates with complex congenital heart disease (e.g., single ventricle, aortopulmonary transposition) has documented maturational abnormalities. The impaired brain development ("cortical dysmaturation") and metabolism of the brain of the fetus and neonate with complex congenital heart disease resemble findings in the preterm infant. This immature status of the brain may predispose these infants to similar vulnerability to white matter/subplate injury as that seen with prematurity (see Vulnerable Cell Populations: The Preterm Infant) [264–267]. However, the patterns of structural and metabolic abnormalities in congenital heart disease also include features distinguishable from prematurity and white matter injury [260, 268]. That is, although white matter defects are the most common injury associated with congenital heart disease, the distribution of white matter injury differs from that seen in the preterm neonate [269], and white matter injury fails to completely explain the neuropathology associated with complex lesions (e.g., decrease brain volumes,

abnormal gyrification, abnormalities in microstructure/connectivity) [270]. For example, reduced total and gray matter volumes have been noted in fetuses with tetralogy of Fallot between 20 and 34 weeks' gestation [271]. In another report, reduced subcortical gray matter volume in term patients with complex heart disease was associated with "poor behavioral state regulation" [261]. Finally, using quantitative MRI and magnetic resonance spectroscopy, detailed associations between subcortical morphology (i.e., thalamus and cerebellum) and white matter metabolism revealed distinct regional patterns of metabolic deficits (i.e., glutamate, citrate, n-acetyl aspartate, lactate, citrate) when preterm control infants were compared with term and preterm infants with complex heart disease [268]. For example, reduced cerebellar volume was associated with reduced glutamine metabolism in the preterm and term groups with congenital heart disease, but not in the preterm control group. Such studies advance the understanding of the complexity of gray and white matter abnormalities in the context of metabolism of the brain in neonates with complex congenital heart disease. From another viewpoint, after documenting aspects of normal patterns of migration from the subventricular zone (piglet model), investigators compared the effects of chronic hypoxia on this process and compared the findings with autopsy specimens from infants with complex congenital heart disease. Of particular significance, a drastic depletion of neuroblasts within the subventricular zone was noted in both groups [270], implying that chronic hypoxia may be a fundamental mechanism for the injury in patients with complex congenital heart disease.

Thus, although conventional brain magnetic resonance imaging documents preoperative injury in the multiple domains, including ischemic infarcts, white matter injury, and other insults in up to 50% of infants with congenital heart lesions that require surgery in the neonatal period, quantitative imagining and spectroscopy are critical to advance the goal of correlating metabolic mechanisms with the structural injury. Also, quantitative MRI techniques contribute to knowledge about the timeline of brain injury. For example, a recent report focused on the "DTI tract-based spatial" technique applied to infants with complex lesions, advancing the possibility of tracking injury with sequential imaging to attempt to document an evolving injury and predict neurodevelopmental outcome [272]. Diffusion tensor imaging (DTI) has been broadly applied to monitor the development of white matter microstructure, especially in the setting of dysmaturation of the immature brain. The technique applies the "properties of water molecules as a window into regional axonal density and white matter integrity" [273]. Specifically, fractional anisotropy (FA) reflects axonal density and integrity of white matter (increases with maturation), and mean diffusivity (MD) measures the diffusion of water molecules (decreases with maturation) [274].

Similar to the preterm infant, the neurodevelopmental outcome of the term infant with complex congenital heart disease reflects a complex interaction between a focal brain injury (e.g., white matter injury) and its profound effects on subsequent brain development [275]. Although the specific mechanism for the in utero delay in development is unclear, disturbances in the fetal circulation with decreased delivery of oxygen and other metabolites to the brain may play a fundamental role [48, 276]. Consistent with this hypothesis, infants diagnosed with complex heart disease prenatally had improved outcomes compared with those who were diagnosed postnatally [277]. That is, delivery of high-level intensive cardiac care preoperatively correlates closely with a fetal diagnosis, thereby improving the likelihood of cardiovascular stability. Similarly, acquired postoperative periventricular leukomalacia in infants with hypoplastic left heart syndrome correlated with the time to surgery after birth [278], implying that the risk for injury may increase with prolonged exposure to the disturbed postnatal cerebral hemodynamics and/or metabolism associated with this critical lesion [279].

Finally, although complex cyanotic heart disease confers a particularly high risk of developmental delay, neurologic abnormalities commonly evolve in children with either acyanotic or cyanotic lesions, especially in those who require surgical intervention in the first few days of life [280].

Summary

That the brain of the 34-week gestation fetus weighs only 65% of that of a term infant (Fig. 2.8) [191] implies dramatic development during the last month of normal fetal life. Overlap in the pathophysiology of lesions common in the preterm infant (periventricular leukomalacia [PVL] and germinal matrix–intraventricular hemorrhage [GM-IVH]) with those most common in the term infant (HIE, arterial stroke) is not surprising. In part, the overlap can be explained by responses to injury in the setting of selective vulnerability of the immature/newborn brain coupled with disturbances in the regulation of CBF.

Autoregulation of Cerebral Blood Flow

Cerebral autoregulation accounts for a constant CBF over a wide range of systemic blood pressure (in adults, between mean arterial pressures 60 and 150 mmHg) [281]. Such a phenomenon implies that changes in perfusion pressure elicit vasoconstriction and vasodilation to maintain a stable blood flow. Various vasoactive factors have been linked to local regulation of CBF (e.g., hydrogen ions, potassium, adenosine, prostaglandins, osmolarity, and calcium) [210].

The term "pressure passive" refers to the disruption of autoregulation so that changes in blood pressure alter CBF. In neonates, especially the very low birth weight infant, pressure-passive CBF is common [282–284] and has been identified as a critical risk factor for central nervous system injury and the subsequent adverse neurodevelopment [285, 286]. That is, even if intact, the range for autoregulation in normal fetal/preterm and term animals and humans is narrower compared with their more mature counterparts.

With rapidly evolving noninvasive monitoring, experts have proposed a variety of systems to monitor autoregulatory function. For example, correlating cerebral oxygenation (via near-infrared spectroscopy [NIRS]) with arterial pressure, investigators noted that autoregulation and "cerebral reactivity" improve over the first 4 postnatal days and served to predict death/severe intraventricular hemorrhage [287]. Recently, using a combination of transcranial Doppler techniques and intra-arterial blood pressure monitoring in preterm infants, experts reported that the regulation of *systolic cerebral blood flow velocity by autoregulation* improved dramatically between 23 and 33 weeks' gestational age [288]. The maturation of autoregulation appears to track the increase in the muscularis layers of the cerebral arteries and arterioles during the third trimester [285, 288]. Similarly, the concept of a "cerebrovascular critical closing pressure" (i.e., the arterial blood pressure at which blood flow to the brain ceases) in the setting of immature autoregulation in the preterm infant has been proposed as relevant to determining "effective cerebral perfusion" (i.e., arterial blood pressure minus the critical closing pressure). Similar to autoregulation, critical closing pressure increases with gestational age (1.4 mmHg/week, between 23 and 31 weeks) [289]. The clinical implication is that cerebral under-perfusion may accompany hypotension. Although this measurement would be challenging to apply routinely in the clinical setting, the developmental pattern of critical closing pressure adds to the understanding of mechanisms of injury in the preterm infant.

Of more relevance to the clinical setting, near-infrared spectroscopy (NIRS) has been widely adapted to measure cerebral hemodynamics and oxygenation, including estimating CBF. A novel adaptation of this technique to quantify autoregulation involves correlating cerebral blood volume (or cerebral oxygenation) and mean arterial pressure to identify the "optimal mean arterial blood pressure" in each patient at a specific time point (e.g., in settings such as cardiopulmonary bypass and after hypoxic–ischemic injury) [285]. For example, loss of autoregulation is implied when blood pressure and cerebral blood volume correlate. Although these algorithms have not achieved everyday clinical relevance, "a bedside monitor capable of demonstrating the function (dysfunction) of the autoregulatory system, aided with the integration of a secondary source of information such as EEG, will allow for personalized blood pressure management, avoiding overtreatment of 'hypotension' in infants with intact autoregulation and enhancing recognition of poor cerebrovascular health in infants with 'normal' blood pressures" [290].

Although normal blood pressure increases markedly during the third trimester, defining "hypotension" has remained controversial, especially in the first day to week of life [148, 149, 291–294], when parameters that influence blood pressure (e.g., afterload, preload, contractility, adrenergic function, and other factors) tend to be variable, unpredictable, and impossible to measure directly [295]. Furthermore, the criteria for treating "hypotension" remain elusive [296–298]. Antihypotensive therapy has neither improved outcomes [299] nor been detrimental [300]. As gestational age decreases, the normal blood pressure in preterm infants is close to the lower limit of autoregulation [293, 301, 302]. As a result, if the arterial blood pressure increases abruptly and/or rapidly, the fragile vessels in the immature brain may rupture (see Germinal Matrix–Intraventricular Hemorrhage). Similarly, hypoxia–ischemia may develop with hypotension. Thus, the CBF of the preterm infant seems to be vulnerable to both hypo- and hypertension.

Greisen posited that in critically ill neonates, cerebral autoregulation should be considered "imperfect," not simply present or absent or "all or nothing." That is, the flat part of the autoregulatory plateau is not horizontal but upward sloping. The slope of this part of the curve defines the degree of disturbance in the autoregulation (Fig. 2.10) [303]. Although the limits of the autoregulatory plateau have not been defined with certainty, the range in the term infant is ~25–50 mmHg (mean arterial pressure), but less and narrower in the preterm infant. Similarly, postnatal age and other factors affect the range and the limits of autoregulation [210]. To complicate matters, metabolic abnormalities common in the neonates (e.g., hypoxia, hypercarbia) impact cerebral autoregulation [301, 304–306]. For example, the series of reports by Lou documented a reduced CBF in the neonate (i.e., 20 mL/100 g/min), and in various clinical settings, cerebral flow changed in response to blood pressure (i.e., disturbed autoregulation) [301, 305].

In the immature human (spontaneously breathing or after 48 h in the mechanically ventilated), with intact autoregulation, the response of CBF to changes in carbon dioxide (4% change for each 1 mmHg in $PaCO_2$) is more robust than to changes in blood pressure (1% change for each 1 mmHg in pressure) [307, 308]. However, such responses are not predictable when autoregulation is markedly impaired, such as in severely asphyxiated infants [309], in response to seizures [310], and, to a less degree, in mechanically venti-

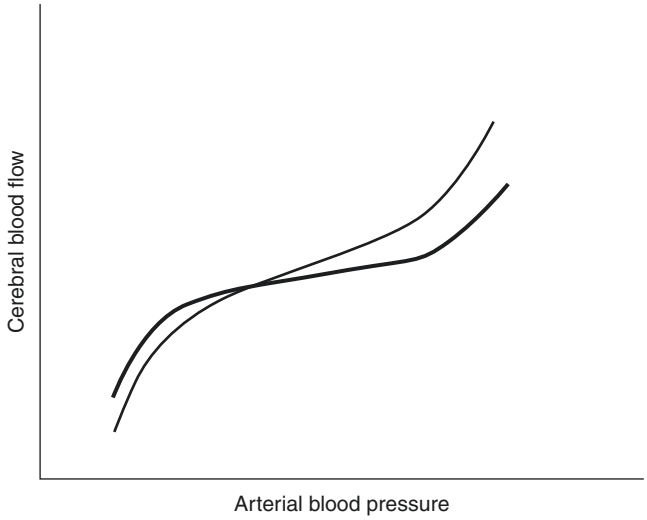

Fig. 2.10 Theoretical concept of autoregulation in the neonate. The flat section of the heavy line represents intact autoregulation, where CBF changes minimally over a range of arterial blood pressure. Below the knee of this curve, CBF decreases as blood pressure decreases. Similarly, above the flat part of the curve, CBF increases as blood pressure increases. Greisen suggests that the flat part of the autoregulatory plateau may never be horizontal and the shape of the curve may change in various clinical scenarios. The degree of the tilt may be the critical clinical factor. He suggests that autoregulation should not be simply considered "present" or "absent" but instead should be approached as quantifiable (from Greisen [303])

lated preterm infants especially in the first day of life [311, 312]. Similarly, routine maneuvers for supportive care in the NICU (e.g., suctioning, administering surfactant) have been associated with disturbed autoregulation [313, 314].

Although impossible to accurately predict and although responses to changes in $PaCO_2$ vary with gestational and postnatal age, neurologic injury, systemic illness, and metabolic derangement, both hypo- and hypercarbia should be considered to have potentially dramatic effects on CBF [315]. In fact, in the neonate, both hypercarbia and hypocarbia have been associated with severe neurologic insults [316, 317]. Hypercarbia in the neonate directly inhibits cerebral autoregulation in preterm infants (500–1500 g) [316]. Similarly, within various developmentally distinct ranges, both hypoxemia and hypoglycemia directly increase CBF [318].

Thus, common therapeutic maneuvers (mechanical ventilation, airway suctioning), metabolic derangements (hypoglycemia, hypercarbia, hypocarbia, hypoxia, hypo-/hypernatremia, and hypocalcemia), the presence of a patent ductus arteriosus, and other insults (seizures, sepsis) may dramatically affect the neonate's ability to compensate for derangements in either hemodynamic or cerebrovascular status. Developing a reliable and simple system to measure CBF seems critical to enhance care to the preterm infant.

Cerebral White Matter Injury

The risk for white matter injury is increased in very low birth weight infants (<1500 g), in that 10–15% develop motor deficits (cerebral palsy), and 25–50% may display cognitive, attentional, behavioral, or socialization problems. Thus, white matter injury in the preterm infant implies long-term motor and cognitive disabilities. The patterns of injuries now include neurons and axons as well as white matter [201, 319, 320].

Recently, the term "white matter injury" (WMI) was proposed to supplant "periventricular leukomalacia (PVL)" [321], since necrosis ("leukomalacia") is absent in the predominate variety of this lesion. That is, on the basis of *neuropathological* studies, cerebral WMI can be stratified into four categories, including three levels of PVL based on severity: necrosis with macroscopic cysts (>5 mm) with loss of all cellular elements ("leukomalacia"), focal necrosis with macroscopic but small (2–3 mm) lesions (i.e., punctate white matter lesions [PWMLs]), and focal necrosis with microscopic (<1 mm) lesions not visible on conventional MRI. Finally, the least severe lesion, without "leukomalacia," includes diffuse white matter gliosis (DWMG) but no focal necrosis [211, 321].

The cystic lesions that typically develop in the deep, periventricular white matter consist of macroscopic necrosis, which eventually evolves into cysts that are easily imaged on cranial ultrasound, but only in <5% of VLBW infants. The diffuse, non-cystic component of PVL (PWML) is generally identified in the more central periventricular white matter, comprises ~15–25% of WMI, and consists of focal, microscopic necrosis not readily identified on cranial ultrasound; 95% of WMI is identifiable on early MRI [211, 322–326]. With advanced MRI techniques, DWMG has been identified in as many as 50% of ELBW infants [321, 322]. Unfortunately, neuropathologic data cannot be definitively correlated with neuroradiologic studies.

On MRI, cysts or PWMLs can be readily visualized, probably representing the more severe categories of PVL. A third category of abnormality has been noted via diffusion-based MRI and includes "excessive high signal intensity diffuse signal abnormality, increased apparent diffusion coefficient, and decreased anisotropy" [324]. This abnormality may occur in isolation but also accompanies the cystic WMI as well as PWML. Whether this lesion represents WMI with gliosis but no necrosis and/or microscopic necrosis is unclear. With advances in neuroimaging, this spectrum of WMI may be more clearly defined and more closely aligned with neuropathology.

Of importance, the timing of MRI impacts the reported incidence of various types of WMI. As cysts evolve into gliotic scars, size diminishes [327]. Similarly, PWMLs vis-

ible at early postnatal scans often are not apparent on term equivalent scans [325, 328]. In contrast, the diffuse high-intensity signal increases with postnatal age. For example, in one report, the incidence of diffuse white matter abnormalities increased with postnatal age, from 21% to 53% and 79% between the first postnatal week and term equivalent [329]. Whether this diffuse lesion correlates with outcome remains controversial [330], but quantitative analyses imply that cognitive function may be correlated [331].

Although white matter injury has been identified in preterm infants for decades, associated gray matter developmental abnormalities have been increasingly recognized over the last two decades as quantitative MRI techniques have evolved. Volumetric analyses have documented neuronal/axonal disease most commonly in the thalamus, basal ganglia, cerebral cortex, and cerebellum. These lesions appear on MRIs performed as early as term equivalent and persist to adulthood [180, 224]. Although the focal, cystic, necrotic lesions of WMI seem to correlate with motor deficits, only a more extensive insult can account for the widespread neurologic insults of the ex-ELBW infant. The non-cystic component of white matter injury may account for the cognitive deficits of ex-premature infants, although the attention deficits and behavior/socialization abnormalities are more likely related to the associated axonal/gray matter injury. Of note, in a recent autopsy study, damage to the thalamus was identified in ~60% of infants with PVL who died early in life [332]. The authors note that the thalamus likely mediates cognition via connectivity with the entire cerebral cortex so that neuronal loss in the thalamus may be a strategic site for cognitive dysfunction in preterm survivors with WMI. Volpe emphasizes that the ultimate clinical outcome from this "panencephalopathy of prematurity" (i.e., white and gray matter injury) evolves not only from the primary injury (e.g., white matter injury) but possibly more importantly from the profound abnormalities in subsequent development [182, 183].

The vulnerability of the immature brain to white matter injury is attributed to a combination of insults: ischemia/disturbed autoregulation and/or infection/inflammation. The border/end zones of the immature cerebral circulation, with incomplete development of both long and short penetrators into the white matter, are inherently at risk for ischemia [333]. The deep focal necrotic lesions of PVL are identified in the end zones of the long penetrating vessels from the middle cerebral artery. Furthermore, the extremely low blood flow in the white matter especially in the first 1–2 days of life adds to the vulnerability of this region of the brain [334]. Global CBF is ~15 mL/100 g/min at this age (compared with the human adult, 45–50 mL/100 g/min). Of importance, flow to white and gray matter can vary significantly. In one study, blood flow to white matter was only 17% of that to the basal ganglia/thalamus [334]. Specifically, blood flow to the white matter is ~25% of that to the cortex, ranging between 1.6 and 3.0 mL/100 g/min [211]. In the neonatal puppy, the decrease in CBF as a result of hypotension differed among various regions of the brain, but the white matter was most vulnerable [335]. In addition to the substantial incidence of hypotension in the preterm infant in the setting of the transitional circulation during the first 48 h after birth, disturbed autoregulation (see Autoregulation of Cerebral Blood Flow) augments the risk for injury from either over- or under-perfusion.

Although hypoxia and/or ischemia stimulates the release of proinflammatory cytokines, a robust relationship between infection (e.g., production of cytokines/free radicals) and WMI remains elusive. Nonetheless, a clear-cut maturation-dependent susceptibility of pre-oligodendrocytes to free radical injury (both reactive oxygen species and reactive nitrogen species) in the presence of iron and decreased antioxidant mechanisms has been documented [204, 211, 326] and associated with axonal hypomyelination (see Vulnerable Cell Populations: The Preterm Infant). Finally, a novel hypothesis suggests that "mitochondrial dysfunction" evolves from such stresses during periods of rapid development, resulting in "arrested cellular differentiation and proliferation" and impaired development, allowing a unifying hypothesis for injury in both the brain and the lung [336].

Thus, the evolution of WMI seems to be multifactorial [319], involving complex interactions of immature cardiovascular, neurologic, and immunologic (and other) factors often in the presence of infection (e.g., neonatal sepsis) or chronic inflammation (e.g., chorioamnionitis), consistent with the "multiple-hit hypothesis" for WMI in the preterm infant (e.g., immaturity, fetal growth restriction, mechanical ventilation, surgery for NEC, male gender) [337]. Hence, vulnerability increases with exposure to multiple risk factors. From the viewpoint of possible treatment, erythropoietin does enhance oligodendrogenesis and the survival of oligodendrocytes (see Vulnerable Cell Populations: The Preterm Infant). Other possible treatments including growth factors (e.g., epidermal growth factor) and mesenchymal stem cells have received attention for possible therapeutic roles, although their mechanisms have not been established [338]. Lastly, a novel therapy in the early stages of evaluation centers on drug-based myelin-enhancing strategies, such as clemastine, a compound that promotes myelination in patients with multiple sclerosis [339].

Germinal Matrix–Intraventricular Hemorrhage

The etiologies of intracranial hemorrhage in the *term* infant generally include trauma, coagulation abnormalities, anatomic anomalies (aneurysm, arteriovenous malformation), and perinatal asphyxia. Overall, the most common etiology of intraventricular hemorrhage, the germinal matrix–intra-

ventricular hemorrhage (GM-IVH), predominantly occurs in the preterm infant, with incidence and severity increasing with decreasing gestational age [196]. The persistent significance of this lesion centers on long-term consequences, as 50–75% of infants develop cerebral palsy, developmental abnormalities, and/or hydrocephalus [340]. Thus, the message in a recent publication remains notable: "Germinal Matrix—Intraventricular Haemorrhage: still a very important brain lesion in premature infants!") [341].

Initially, GM-IVH was divided into categories that correlated with the severity, extent of the initial injury, and the clinical outcome. The lesions were classified based on data from *computerized tomography* [342]. In this context, grade I refers to a subependymal hemorrhage with minimal or no IVH (i.e., restricted to the germinal matrix) and grade II implies an IVH into a lateral ventricle without distention. Grade III IVH includes enlargement of the ventricles by intraventricular blood. In this classification, a grade IV hemorrhage involves ventricular dilatation and hemorrhage into the parenchyma of the brain.

After correlating the severity of the GM-IVH with the extent of hemorrhage in the lateral ventricle on the *parasagittal cranial ultrasound*, the grading system was revised. In grade I, the hemorrhage is limited to the germinal matrix, and ventricular enlargement is less than 10%. In grade II, 10–50% of the ventricle is filled with blood. In grade III, more than 50% of the ventricle is involved, usually with enlargement of the lateral ventricles. Grade IV was eliminated, and instead, the term periventricular hemorrhagic infarction (PVHI) was introduced to describe an echo density of the periventricular parenchyma secondary to hemorrhage [343]; this lesion is distinct from GM-IVH. Thus, in the former classification, intraparenchymal lesions were labeled grade IV GM-IVH, hypothesizing that the IVH had extended from the ventricle laterally into the white matter. The latter classification emphasizes that the pathophysiology of PVHI is a hemorrhagic venous infarction (see below), not simply a massive GM-IVH. However, many experts continue to refer to a PVHI as grade IV IVH. Based on three factors, PVHI is stratified further according to severity: size (localized vs. extensive), unilateral versus bilateral, and evidence of midline shift [343, 344].

Overall, the incidence of GM-IVH has remained remarkably stable over the last two decades [340], ranging from 7% to 23% [345], but in ELBW, it may occur as frequently as 30% (750–1,000 g) to 40% (501–750 g) [8]. In this same large cohort of the NICHD Neonatal Research Network, in 2000–2002, the incidence of severe IVH (grade III) and PVHI was 16% and 24%, respectively. In another cohort, the overall incidence of GM-IVH decreased from 42% (1982–1989) and 22% (1990–1999) to 22% between 2000 and 2002. The incidence of severe GM-IVH also decreased from 15% to 2% [346]. From another perspective, although the incidence declined since the 1980s, with improved survival of the ELBW, the absolute number of cases remains high [347]. In this recent meta-analysis, the incidence in all infants <1500 g ranged between 25% and 30% but as great as 45% in those <1000 g.

Although substantial in infants with PVHI (~50%), in early studies, grade I–II bleeds did not seem to affect mortality in preterm infants [348]. A recent meta-analysis (*infants <34 weeks' gestation*) describes a greater odds of death or moderate to severe neurodevelopmental impairment associated with mild IVH, with greater odds in those with severe IVH [347]. Thus, increasing severity of IVH may be associated with adverse long-term neurodevelopmental outcomes, but mild IVH alone may impact outcomes compared with infants without IVH. Of note, while severe neurologic sequelae are rare in *near-term* infants with uncomplicated grade I or II IVH, developmental functioning [344] is abnormal, and gray matter volumes are 16% less than predicted based on MRI [349]. In *ELBW infants*, data for outcome after low-grade IVH are controversial [350]. For example, while some recent reports document increased rates of neurosensory impairment, developmental delay, cerebral palsy, deafness at 2–3 years [351], and long-term neurodevelopment impairment [352], some experts continue to contend that low-grade hemorrhage is benign [353]. Finally, similar to earlier reports, recent data (infants <27 weeks' gestation) from the Eunice Kennedy Shriver National Institute of Child Health and Human Development Neonatal Research Network noted that, compared with neonates with normal cranial ultrasounds, *nonhemorrhagic ventriculomegaly* (i.e., no GM-IVH) was associated with a two- to threefold greater odds of abnormal neurodevelopment, cognitive impairment, moderate to severe cerebral palsy, and death or neurodevelopmental impairment (but not death alone) [354].

Because WMI is more accurately assessed via MRI, data based solely on ultrasound may be difficult to correlate definitively with outcome [355]. In contrast to GM-IVH, PVHI often is a devastating lesion [351]. For example, in one report, two-thirds of survivors of PVHI had motor delays, and one-half had cognitive impairment, with visual field abnormalities in one-third and epilepsy in 20%. After a PVHI, 90% of infants have poor neurodevelopmental outcome [356]. Similarly, a recent analysis noted moderate-to-severe neurosensory impairment in ~40% of grade III and grade IV (PVHI) hemorrhage [351]. Finally, posthemorrhagic hydrocephalus severe enough to require a ventricular–peritoneal shunt is associated with severe neurocognitive impairment in early childhood in 78% of those with grade III lesions and 92% in those with a PVHI [345].

At least in part, the pathophysiology of GM-IVH is related to the structure of the immature brain. The anatomy of the germinal matrix, the site of bleeding in this lesion (usually between the caudate nucleus and the thalamus at the level of

the foramen of Monro) [343], also contributes to the greater risk for hemorrhage in the preterm neonate. Proliferating ventricular and subventricular areas of the germinal matrix (most prominent at the head of the caudate nucleus) produce neuroblasts (cerebral precursors for both gray and white matter) and glioblasts primarily between 10 and 20 weeks (but as late as 36 weeks). Reflecting on the great metabolic demand associated with rapid angiogenesis, the germinal matrix is densely cellular and vascularized. But the region is gelatinous, with poor support for the vascular network. That is, sparse support of microvessels with astrocyte end feet, decreased number of pericytes, reduced fibronectin, and immature tight junctions define the intrinsic vulnerability of the germinal matrix [340]. The gelatinous nature of the area gradually decreases with increasing age, with maximum volume at 25 weeks but being barely present in term infants.

This dense vascular network arises from the middle and anterior cerebral and anterior choroidal arteries that enter into a bed of immature, large, irregular capillary-like vessels and eventually drain into the deep venous system from the brain. The specific vulnerability of the immature neurovasculature to GM-IVH correlates with the delayed development of the venous drainage compared with the arterial system. The immature veins are thin-walled with a branching pattern predisposed to collapse. Because the superficial veins are underdeveloped, most cerebral venous drainage depends on the deep venous system that drains the germinal matrix and most of the white matter.

The veins join, forming the terminal vein, which makes a "U-turn" near the head of the caudate nucleus to join the vein of Galen. Thus, the "terminal vein" courses within the germinal matrix and makes an abrupt change in course at the common site of GM-IVH. Because of this unique anatomy, a large GM-IVH may obstruct the terminal vein, leading to venous distension, ischemia, and rupture, producing a PVHI. Thus, PVHI either accompanies or follows but never precedes a large GM-IVH and, if the GM-IVH is bilateral, the PVHI is always ipsilateral to the side of the larger hemorrhage [343].

The primary site of bleeding in the preterm brain is the junction of the veins and capillaries, rather than at the junction of the arteries/arterioles and capillaries. Between 24 and 28 weeks' gestation, the germinal matrix is most prominent at the body of the caudate nucleus and between 28 and 32 weeks resides at the level of the head of the caudate, involuting by ~36 weeks' gestation [343, 357]. When hemorrhage extends from the germinal matrix into the ventricles, blood spreads throughout the ventricular system possibly causing arachnoiditis and obstructive hydrocephalus. The free iron that is released from hemoglobin may produce hydroxyl free radicals (Fenton reaction; see Age-Related Patterns of Injury) [234], in addition to other free radicals that are generated during hypoxic–ischemic injury. Ideally, antioxidant systems (e.g., superoxide dismutase; glutathione peroxidase; catalase; vitamins A, C, and E; beta carotenes; glutathione) are robust and redundant to effectively scavenge free radicals. However, when excess free radicals are generated, stores of antioxidants are depleted. In that setting, the downstream effect is cell membrane damage, increased intracellular calcium, and eventually cell death. The neonatal brain encounters increased risk for injury secondary to the combination of high oxygen consumption coupled with a reduced concentration of antioxidant systems [212].

Coincident with the often-tumultuous events characterizing the transitional circulation including the large incidence of hemodynamic instability over the first few days of life, 50% of GM-IVHs are diagnosed by day 1 and 90% by day 4 [357]. The large incidence of pressure-passive CBF correlates with GM-IVH (see Autoregulation of Cerebral Blood Flow) [358]. In the presence of pressure-passive flow and because both the periventricular white matter and the germinal matrix lie within arterial end zones, both areas are at great risk for ischemia during periods of decreased cerebral perfusion and for rupture during periods of increased flow. Reperfusion after ischemia may contribute to excitotoxic injury [359]. Thus, in the presence of disturbed autoregulation, noxious stimuli (e.g., airway suctioning, painful procedures such as surgery), commonly associated clinical problems (severe respiratory distress syndrome, pneumothorax, seizures, patent ductus arteriosus, infection), rapid delivery of intravenous fluids, and metabolic disturbances (e.g., hypoglycemia, hypoxia, and hypercarbia) [306] may precipitate an acute increase in arterial and/or venous pressures that may contribute to a GM-ICH. In the opposite direction, hypotension from a variety of insults (e.g., asphyxia, anesthetic agents, sepsis, hypocarbia) may cause alternating cycles of decreased CBF and reperfusion. Finally, positive pressure ventilation or pneumothorax can abruptly increase central venous pressure, impeding cerebral venous drainage, possibly increasing the risk for venous hemorrhage. Of interest, no events during pregnancy have been definitively linked to postnatal GM-IVH [360, 361]. *Finally, the relationship between inadequate function of various mechanisms of coagulation to GM-IVH remains of interest but poorly defined* [362].

Thus, although WMI (e.g., nonhemorrhagic, symmetrical) and GM-IVH (hemorrhagic, nonsymmetrical) are characterized by distinct pathophysiology, the underlying etiologies overlap and are related to the combination of immature cardio- and cerebrovascular function in the presence of vulnerable anatomy and age-specific metabolic requirements. Not surprisingly, WMI and GM-IVH are commonly identified on the same MRI.

Cerebellar Injury

In addition to the pervasive neuronal/axonal disturbances involving the cerebral cortex, thalamus, and basal ganglia of neonates secondary to PVL and GM-ICH, the cerebellum has recently been identified as highly vulnerable to injury. "From 24 weeks to 40 weeks of gestation, the cerebellum undergoes a rate of growth nearly unparalleled elsewhere in the brain" (Fig. 2.9). The surface area of the cerebellar cortex increases more than 30-fold during this period [195]. Of particular relevance to the preterm infant, cerebellar development accelerates between 20 and 30 weeks of gestation.

As with other neurologic injuries in the neonate, the incidence of insults to the cerebellum is inversely related to gestational age and can be attributed to two etiologies: destructive (hemorrhage/infarction) and impaired development. For example, the incidence of hemorrhage varies with the type and protocols for imaging, ranging from 9% to 19% (various ultrasound-based imaging with or without MRI) [363] and, more recently, 37% (MRI) [254]. Similar to GM-IVH, cerebellar hemorrhage is usually unilateral, with 77% associated with supratentorial lesions (mostly white matter injury) [195]. In contrast, in a cohort of <33-week gestation infants, cerebellar hemorrhage was more common than WMI, not directly associated with WMI, and more common in the most immature infants [364]. Pathophysiologically, this injury remains incompletely defined.

Impaired cerebrovascular autoregulation predictably contributes to the pathogenesis. For example, in a group of ex-ELBW infants with cerebral palsy, 64% (32/50 patients) had parenchymal cerebellar loss which coexisted with cystic PVL and/or cerebral white matter loss [365] or IVH [366], suggesting a common etiology (i.e., ischemia, infection/inflammation) [367]. Of note, the germinal matrix is present in the cerebellum in the roof of the fourth ventricle and has been referred to as a "secondary germinal matrix" [368]. Destructive lesions can be confined to the cerebellum, and infants can be asymptomatic until delayed development is noted months to years after birth [369]. In those with severe destructive injuries, the impact on function can be significant, including spastic–ataxic–dyskinetic cerebral palsy, severe cognitive deficits, microcephaly, and epilepsy [370].

In other cases, MRIs reveal cerebellar underdevelopment (unilateral or bilateral symmetric deficits in cerebellar volumes) without destructive lesions [371] but in association with supratentorial lesions (i.e., PVL and/or GM-IVH). Injury to granular cells (e.g., secondary to injury from free iron after hemorrhage) [371] is significant not only because of decreasing this population of cells but also because of disturbing the excitatory input to other cells (e.g., Purkinje cells) that disrupts the development of the intricate cerebellar circuitry [195]. The association of cerebellar underdevelopment with supratentorial lesions suggests the role of "multiple remote tropic transneuronal interactions" [195]. For example, unilateral PVHI may be associated not only with an expected loss of ipsilateral cerebral volume but also with loss of contralateral cerebellar volume; similarly, unilateral cerebellar hemorrhage is associated not only with decreased ipsilateral cerebellar volume but also with decreased contralateral cerebral volumes. Bilateral primary injury in the cerebrum is associated with secondary bilateral injury in the cerebellum and vice versa. Similarly, the development of the pons is associated with cerebellar injury, perhaps secondary to degeneration of pontocerebellar tracts [367]. Volpe suggests, "an intact reverberating circuit between cerebrum and cerebellum and vice versa may be especially critical for normal growth during this critical phase of development" [195]. Recently, the development of the microstructure of the cerebellum is disturbed in preterm infants at term equivalent age (<32 weeks' gestation) compared with healthy term infants [372], but the clinical correlate is unclear. Consistent with other studies [373], some experts note that preterm birth more significantly reflects brain injury and comorbidities rather than simply gestational age [273].

In the setting of impaired cerebellar development, long-term outcome includes deficits in executive functions, visual–spatial functions, and language [374]. Others have documented disturbances in expressive language and socialization [375]. The complex role of the cerebellum extends beyond motor function, as this area of the brain provides integral effects for cognitive and emotional development. Cerebellar injury is associated with significant neuromotor and intellectual deficits, as well as learning, language, and social behavior deficits. That is, cerebellar injury can result in cognitive and affective disturbances, including socialization difficulties and some positive autism findings [376]. Finally, a "cognitive–affective disorder" (executive, visual–spatial, linguistic, affective deficits) has been described in older children and adults with cerebellar injury [377, 378]. Thus, abnormalities in cerebellar developmental may cause cognitive, language, and socio-affective abnormalities in the ex-premature infant.

Clinical Significance and Summary

Many characteristics of the immature neurologic system predispose the neonate to injury in the predictably labile intraoperative period. Disturbed autoregulation combined with vulnerable populations of cells in the setting of labile hemodynamic and respiratory status in the perinatal period without a reliable system for monitoring cerebral perfusion demands that neonatal anesthesiologists focus on defining "normal" preoperatively for each infant and attempting to maintain that status intraoperatively. Although easy to recommend, avoiding wide fluctuations in blood pressure,

$PaCO_2$, and PaO_2 is almost impossible, especially in the intraoperative setting when cardiorespiratory instability is common. Hemorrhage often requires rapid infusions of crystalloid and colloid, which can inflict neurologic injury in the setting of disturbed autoregulation and fragile vasculature. NIRS may eventually function as a trend monitor, but currently, artifacts are notoriously common.

The Pulmonary System

Moving from fetal to postnatal life requires an abrupt and dramatic transition from complete dependency on the placenta for gas exchange to air-filled, perfused lungs within seconds after birth. For preterm or asphyxiated infants or in the setting of anomalies associated with cardiorespiratory dysfunction (e.g., congenital diaphragmatic hernia, tracheoesophageal fistula, some types of congenital heart disease), the superimposed effects of surgery, inhalational anesthetics and other medications, positive pressure ventilation, and infection add to the critical short-term challenge of achieving postnatal physiologic stability without incurring long-term morbidity.

Embryology

Based on morphology, the development of the pulmonary system includes five morphologically and biochemically defined (but somewhat overlapping) stages (embryonic, pseudoglandular, canalicular, saccular, alveolar) [379] (Fig. 2.11). Knowledge of the sequence of developmental events can inform estimates of the timing of congenital malformations [380] that result from fetal–maternal factors (e.g., oligohydramnios), genetics, or developmental insults [381].

Development of the lung includes a tightly regulated, complex, interactive process involving epithelium, mesenchyme, and endothelium. Recently, investigators have increasingly recognized that the differentiating alveolar epithelial cell is regulated by the simultaneously differentiating capillary endothelial. This has led to a newly identified process, "angiocrine signaling," that refers to an "endothelial, cell-driven active paracrine function of blood vessels on organ development and regeneration mediated by the organ-specific microvasculature." That is, pulmonary endothelial–epithelial interactions govern pulmonary development, and "regeneration is driven by growth factors derived from blood vessels that trigger epithelial differentiation." Growth factors from blood vessels induce epithelial differentiation and, therefore, development and, at other times, regeneration [382].

Intense investigations into the molecular basis of development have ventured into the closely related topic of "regeneration." The capacity and function of various progenitors in the postnatal lung, especially in the setting of injury, are central to the concept of "outcome" after critical events such as preterm birth. Understanding the complex pathways during development is central to the question of "whether the pathways that govern the differentiation of these progenitors during development are reactivated upon injury." Such data contribute to innovative targeting to treat preterm infants and those with congenital anomalies and pulmonary dysfunction [383].

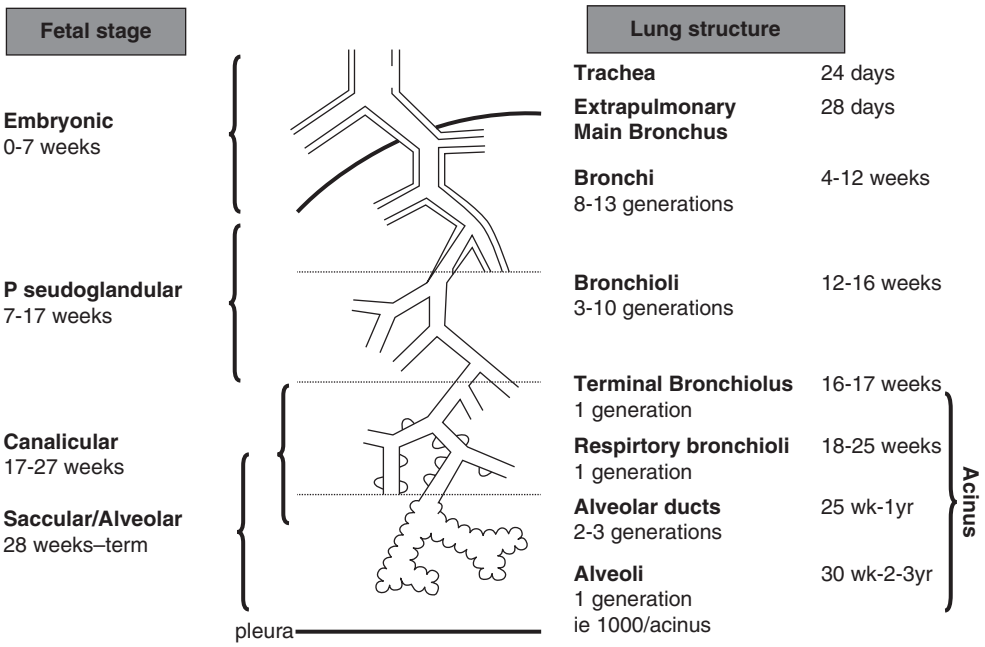

Fig. 2.11 Stages of normal lung development with the airway structure developing within each stage (from Kotecha [381])

The Embryonic Stage (0–7 Weeks' Gestational Age)

At 3–4 weeks' gestational age, the laryngotracheal grove first appears as a ventral diverticulum from the primitive foregut, lined by epithelial cells of endodermal origin [380]. During the embryonic stage, the large airways first appear as epithelial cells from the foregut that eventually invade the mesenchyme to form the trachea. This structure then undergoes a series of branching events [384], requiring the interaction of epithelial and mesenchymal cells [385]. By the fifth week of gestation, the branching has advanced to the level of lobar and segmental bronchi [384], so that five pulmonary lobes have been formed. By the end of the embryonic stage, the 18 major lobules are easily recognized [386]. Although the airway epithelium resembles that of the esophagus at this stage, throughout development, differentiation, and maturation, the primitive endodermal cells produce the population of epithelial cells that characterize the adult lung [384]. During the embryonic stage, the pulmonary vasculature develops in parallel with the airways. At 4 weeks' gestational age, endothelial cell precursors around the developing lung bud eventually form endothelial tubes that continuously coalesce to form the intrapulmonary arteries [387]. Congenital malformations associated with events during the embryonic stage involve the large airways and/or whole sections of the lungs and include pulmonary agenesis, ectopic lobes, lobar cysts, agenesis, malformation, stenosis, or malacia and vascular malformations [380].

Pseudoglandular Stage (7–17 Weeks' Gestational Age)

The most rapid branching of the airways occurs during the pseudoglandular stage. As the epithelial cells divide, the surrounding mass of gland-like mesenchyme [381, 384] regulates the branching. The mesenchyme inhibits branching in the trachea but induces branching in the bronchi [388]. By 14 weeks' gestational age, 70% of the airways present at birth have formed, and by 17 weeks, the conducting airways, terminal bronchioles, and primitive acini are completely established [381]. In parallel with the development of the airways during the pseudoglandular stage, the vascular structures branch rapidly leading to the formation of the pulmonary arteries and veins, which, along with the airways, are derived from mesenchymal tissue [380, 387]. Further differentiation of the pseudostratified epithelium of the airway involves its progressive replacement with columnar cells proximally and cuboidal cells distally. Between 11 and 16 weeks' gestation, ciliated epithelium appears and airway mucus is first synthesized [384]. The cuboidal cells eventually mature into type II pneumocytes. Insults during this stage of lung growth can alter bronchial growth patterns, producing lesions characterized by poor lung growth (pulmonary hypoplasia), sequestration lesions, and congenital pulmonary airway malformations (formerly, cystic adenomatoid malformation) [380].

During this critical period of lung growth, the musculotendinous, dome-shaped diaphragm develops, which, in addition to becoming the primary muscle of respiration, serves to separate the pleural and peritoneal cavities and promote pulmonary growth [389]. At the end of the third week of gestation, the diaphragm consists of a collection of mesodermal tissue, the septum transversum, which separates the pleural–pericardial cavity from the peritoneal cavity. Of note, pleural–peritoneal canals allow limited but persistent communication between these two cavities [389, 390]. The septum transversum migrates downward from the level of the occipital and upper cervical somites (C3) to the level of the thoracic somites by the sixth week of gestation and L1 by the eighth week [389]. During the descent, the neural tissue of C3–C5 origin penetrates the mesoderm and eventually develops into the phrenic nerve. At approximately this time, the right and left pleuroperitoneal membranes close the communication between pleural and peritoneal cavities [389]. As elucidated in murine models, muscle precursor cells migrate laterally to form the lip of the primitive diaphragm and then radiate throughout the developing diaphragm accompanied by new branches of the phrenic nerve [390].

Congenital diaphragmatic hernia (CDH) results from the failure of complete separation of the pleural and peritoneal cavities. At 10–12 weeks' gestation, before the bowel returns to the abdominal cavity from the amnion (where it resides in early gestation), closure of the diaphragm is complete. If the separation of two body cavities is incomplete, the bowel enters the chest, the path of least resistance. However, the bowel then occupies space needed for lung growth. A posterolateral CDH (Bochdalek hernia) results from failure of closure of the pleural–peritoneal membranes, accounts for 95% of diaphragmatic hernias (approximately 1/2,000–1/4,000 live births) [391, 392], is usually unilateral (78% on the left, 20% on the right, 2% bilateral) [391], and often is associated with significant ipsilateral pulmonary hypoplasia as well as abnormal development of the contralateral lung [393]. In addition to abnormal lung development, other anomalies not directly related to the hernia often accompany this lesion (e.g., congenital heart disease, central nervous system anomalies) [391]. The etiology of CDH is not clear, but genetic associations have been noted (e.g., chromosomal aneuploidy) [394] (for a review, see [395]).

Intrauterine exposure to teratogens affecting the retinoic acid enzyme pathway induces CDH through malformation of the primordial nonmuscular diaphragmatic tissue as early as the fifth to seventh weeks of gestation via a cascade of events that leads to failure of closure of the posterolateral

walls in later gestation [390, 396]. Of note, experiments in transgenic mice caused hypoplastic lung development without causing CDH, prompting investigators to conclude that CDH is a primary event [397, 398].

Canalicular Stage (17–27 Weeks)

During the canalicular stage, the distal airways develop into primary acini, consisting of respiratory bronchioles, alveolar ducts, and rudimentary alveoli. The surrounding capillaries develop in parallel [386]. These represent the first units of gas exchange.

Epithelial cells differentiate into types I and II pneumocytes, with type I cells incorporated into the first alveolar–capillary barrier. Surfactant can be detected at approximately 24 weeks with active production beginning at 26–28 weeks. After 26 weeks' gestation, respiratory saccules lie in close contact with pulmonary capillaries, increasing the likelihood of adequate gas exchange essential for extrauterine viability. Before this developmental age, gas exchange may be compromised because of inadequate surface area and function of the lung parenchyma and/or vasculature [379]. For example, survival after birth during the canalicular stage, in part, is determined by surfactant deficiency (respiratory distress syndrome) (see Respiratory Distress Syndrome, below). Although delivery of exogenous surfactant can improve neonatal lung function, subsequent insults associated with supportive care of the preterm infant (e.g., supplemental oxygen, mechanical ventilation, infection) often result in pulmonary hypoplasia or acinar dysplasia [380] and later bronchopulmonary dysplasia.

Saccular Phase (28–36 Weeks' Gestation)

An increase in the surface area of gas exchange is the major feature of the saccular phase of lung growth [380]. The peripheral areas of the lung enlarge, as the acini dilate and the acinar walls thin. Gas exchange is further facilitated as type II pneumocytes increasingly differentiate into type I cells and capillaries develop in close approximation [386].

Alveolar Phase (36 Weeks' Gestation Until ~2–3 Years)

During the alveolar phase, the surface area for gas exchange increases as alveoli septate and increase in number, a process that continues through the third year of life [381, 387]. Type II pneumocytes proliferate and become prominent after 34–36 weeks of gestation. The key feature of type II pneumocytes is eosinophilic lamellar bodies, specialized vesicles that store and release surfactant lipids and proteins [399]. At term, the total number of alveoli in the healthy infant is only 20–50 million [386], increasing to adult numbers of more than 300 million per lung, by 2–3 years of age [400, 401]. Developmental abnormalities during the alveolar phase can result in respiratory distress syndrome, chronic lung disease (see below), and dysplasia of the acini or alveolar capillaries [380]. Although rare, several genetic disorders can also adversely affect lung development, such as mutations in the surfactant protein system [386].

The molecular basis of the control of lung development is incompletely understood, but involves simultaneous, interrelated, reciprocal molecular signaling pathways in the airway and the blood vessels, under the regulation of various transcription and growth factors [380, 382, 383] (e.g., vascular endothelial growth factor [VEGF] and fibroblast growth factors). The surrounding mesenchyme appears to direct the developing epithelial cells, and the mesenchymal–epithelium interactions seem to be essential for normal development [386]. Similarly, the interaction of differentiating alveolar epithelial cells with capillary endothelium plays a critical role. A vascular plexus can be identified as soon as the first lung buds arise from the foregut endoderm [382]. During the alveolar phase, the formation of vascular networks requires alveolarization but the reverse is also true. That is, inhibition of VEGF leads to lung hypoplasia [402]. Of note, hypoxia has been identified as the primary trigger of this late-stage lung development (epithelial branching) mainly via the VEGF (and other angiogenic factors) and HIF-2α and HIF-1α (hypoxia-inducible factors) in stimulating angiogenesis [403, 404].

A variety of mechanical factors affect lung growth in utero and postnatally [33, 380]. For example, in animal models, inadequate fetal lung fluid secondary to a deficiency of amniotic fluid can induce pulmonary hypoplasia [405, 406]. In humans, pulmonary hypoplasia is prominent in the oligohydramnios sequence ("Potter's syndrome") associated with low urine output secondary to renal dysgenesis [407]. Similarly, oligohydramnios secondary to chronic leakage of amniotic fluid can interfere with lung development [408]. Finally, the role of maintaining adequate lung volume with fluid in promoting lung growth and development during the canalicular and saccular stages is the basis of various fetal therapeutic interventions (e.g., in utero tracheal occlusion) intended to induce lung growth in the presence of CDH [380, 409].

Detectable by 10 weeks' gestation, fetal breathing may contribute to maintaining sufficient lung volume and, therefore, growth of the lung, possibly by activating stretch-mediated release of growth factors [380]. That is, "the primary function of fetal breathing is to provide intermittent stretch for structural development of the lung" [410]. When fetal breathing is ablated in animals, lung growth decreases

[411, 412]. Decreased fetal breathing movements may underlie the pulmonary hypoplasia associated with some neurologic disorders, abdominal wall defects, and in utero exposure to certain substances (e.g., chronic exposure to diazepam and, possibly, maternal smoking) [413]. Although lesions occupying the intrathoracic space (e.g., CDH, congenital airway malformations) and skeletal defects involving the thorax can impede lung development secondary to obvious mechanical effects, these anomalies may also impair fetal breathing, which may exacerbate the primary effect of the space-occupying lesion [413].

Postnatal Development of the Lung

Postnatal development of the lung focuses on completing the alveolar stage [414] to achieve maturation of both the airway and microvascular. Of importance, alveolar–capillary microarchitecture transforms from double to single capillary networks [415], and the adult number of alveoli (300–600 million) is established. Although the most dramatic structural processes take place in utero and during the first 1–3 years of postnatal life, recent studies suggest that the bronchioles and alveoli continue to grow in size, number, and complexity beyond adolescence into young adulthood [416–418]. Of importance, patterns of postnatal lung development seem to be linked to in utero and neonatal events. For example, although maximal lung volume is generally achieved by 22 years (30-fold increase in lung volume and 20-fold in gas-exchanging surface area compared to values at term birth), infants with abnormal function secondary to in utero events, prematurity, or neonatal insults may never achieve this "normal" peak. Also, this same group may have a more rapid decline than what normally occurs during the third decade [419, 420]. That is, lung function seems to follow a similar centile over time, tracking from newborn to adulthood [33, 420–423]. Recent studies noted that the pattern of wheezing and lung function do not change noticeably in children who develop "asthma-like" symptoms by 3–6 years of life [420]. Thus, prematurity and/or other insults (e.g., infection, anomalies) can severely impact the growth of both alveoli and vasculature with lifelong consequences [33, 36, 381, 419, 424–426].

Although in utero infection (e.g., chorioamnionitis) and markers of lung inflammation have been associated with an increased incidence of lung injury characterized by poor development [427, 428], the data to establish a direct link between preterm birth and/or injury remain controversial [33, 429, 430]. Similarly, exposure to oxygen seems to increase the risk for BPD [425], but as an independent factor, its role is small compared with the impact of gestational age [431]. On the other hand, although a lifesaving therapy, mechanical ventilation appears to impair normal lung development, resulting in abnormal vascularization and alveolarization [33, 425, 432]. Defining the pathophysiology of postnatal lung growth, especially after in utero and/or neonatal injury remains an "evolving database." Over the last 10–20 years, the definition of BPD and long-term outcomes associated with prematurity have changed [433–435]. Nonetheless, with no dramatic decrease in the incidence of bronchopulmonary dysplasia as the survival of those at the edge of viability increases, morbidity among ELBW infants, especially those less than 25 weeks' gestation, remains significant [419, 435–439]. Of note, the reactive airways associated with prematurity differs from that associated with "asthma" [440].

Oxidative stress has also been implicated in disorders of lung growth (see Oxygen Therapy, below). Other physiologic events associated with prematurity, such as patent ductus arteriosus and immune dysfunction, are also associated with growth disorders [381]. Probably of more importance, postnatal nutrition (e.g., breastfeeding) and a wide variety of environmental toxins (e.g., smoke, air pollutants, alcohol, vitamins) contribute to the overall prognosis for normal growth and development [33, 441]. Of interest, in preterm infants, rapid weight gain in early infancy has been associated with an increased risk for asthma [442].

Because of the recurring theme of "inflammation" as a fundamental mechanism for the increasing risk of BPD, therapy with corticosteroids has had a chaotic history in the context of the ELBW infant. The role of early (<8 days) [443] and late (>7 days) [444] treatment including different systemic drugs and various modes of delivery has been repeatedly tested, but a clear consensus remains elusive [445]. The conflict is that, although anti-inflammatory, these agents also disturb development both in the lung [36, 380] and the brain [446], but the disturbances vary with the agent and timing of postnatal treatment. For example, early systemic dexamethasone was associated with abnormal neurodevelopment but early low-dose hydrocortisone was not [443]. That is, hydrocortisone decreased mortality and reduced rates of patent ductus arteriosus and death/bronchopulmonary dysplasia without long-term complications. In contrast, the trials initiating late treatment were associated with a benefit-to-risk ratio that did not support intervention. Instead, the authors recommend reserving this for the clinical scenario of infants who fail to wean from mechanical ventilatory support but to minimize the dose and duration of treatment [444]. Similarly, other investigators suggest tailoring treatment by following a model that predicts risk for BPD [431]. Consistent with these data, the American Academy of Pediatrics recommends **that "early hydrocortisone treatment may be beneficial in a specific population of patients; however, there is insufficient evidence to recommend its use for all infants at risk of BPD… existing data are insufficient to make a recommendation regarding treatment with high-dose hydrocortisone"** [447]. The academy reaffirmed this statement in 2014.

Recent reports [448, 449] and reviews [450–452] of the effectiveness in decreasing BPD after *inhaled* steroids have revived interest in these agents in establishing an effective but low-risk intervention to prevent BPD (see Respiratory Distress Syndrome). Although not endorsed for routine therapy, intra-airway delivery may offer benefits while avoiding the significant negative side effects on growth associated with other modes of administration, but these data are not yet established [445].

Maternal smoking has been linked to long-standing respiratory disorders during infancy, beginning with its association with intrauterine growth restriction/low birth weight. These respiratory problems may improve in later childhood, but also are likely to persist into adulthood, becoming apparent as normal aging decreases lung function [453–455]. Both prenatal and postnatal secondhand exposures to smoke are linked to structural changes in the developing lung, with altered airway geometry and size (smaller lung with fewer, larger alveoli and low capillary density) [456], increased wheezing [457] with respiratory infections, as well as variable decreases in forced expiratory flows, possible increases in airway responsiveness and bronchospasm, and increased airway resistance (see [453] for a review). This correlation of an impaired capacity for gas exchange predicting reduced exercise tolerance in later life and a more rapid rate of decline in pulmonary function is consistent with the "developmental origins of adult disease" [441, 458]. At least in part, the susceptibility to the effects of smoking may be related to various genetic variants (CYP1A1, GSTT1) [33].

Similar to the close relationship of the parenchyma and blood vessel during normal development, the pulmonary vasculature is co-injured postnatally secondary to prematurity and its associated treatment (i.e., oxygen, ventilatory support). Preterm infants with BPD have increased pulmonary arterial and venous smooth muscle, and infants born before 27 weeks' gestation age often develop hypoplasia and dysplasia of the alveolar capillaries [387]. Although in retrospective studies the incidence of pulmonary hypertension in infants with BPD ranged from 14% to 38%, a recent meta-analysis documented an incidence of 20–25% among ELBW infants. Pulmonary hypertension seems to track the severity of BPD [459]. The pathophysiology of these co-dependent disorders seems to center on the effects of an incompletely defined inflammatory insult [460, 461]. The correlation of BPD with pulmonary hypertension is not surprising; the associated high morbidity and mortality have been documented [462].

Recent guidelines recommend routine screening of patients with BPD for pulmonary hypertension with echocardiogram [463, 464], but the diagnostic criteria and treatment regimens remain incompletely defined but recently updated [465]. Of note, some infants develop pulmonary hypertension without BPD, so that screening may be indicated for a broader group of preterm infants. Similarly, some suggest that screening should be conducted both early and later in the course of the ICN stay since the timeline for developing seems to extend beyond the early postnatal period [461]. Despite the substantial morbidity, the natural history of infants with BPD associated with pulmonary hypertension often is resolved within the first year of life. However, the prognosis for those with persistent pulmonary hypertension is not favorable [462].

Although research in neonatal clinical care must focus on preventing prematurity and lung injury, until that is achieved, the short-term goal remains to minimize the long-term morbidity of prematurity and its associated lung injury exacerbated by critical therapies, such as mechanical ventilation and supplemental oxygen [383, 419, 466–469]. Also critical is a clearer understanding of the impact of "developmental origins of adult disease" to allow intervening in early postnatal development before irreversible injury. With data supporting a link between neonatal and later pulmonary function, systems to streamline the transition from pediatric to adult care remain underdeveloped but deserve scrutiny, since the innate function as well as effects secondary to injury inflicts lifelong functional deficits [420, 421, 423, 440, 470, 471].

Airway Anatomy

Neonatal airway anatomy differs from that of the adult with significant implications for the anesthesiologist (see Chap. 5). With a relatively large head and prominent occiput, both flexion and hyperextension of the neck may obstruct the small, compliant airway (i.e., easily compressible) [472]. Moreover, this anatomy implies that the infant maintains a natural "sniffing position." This eliminates the need to place a support under the occiput to facilitate tracheal intubation. Finally, the tongue of the neonate is large relative to the size of the mouth, which may predispose to obstruction of the upper airway during mask ventilation and difficulty in retracting it during laryngoscopy and tracheal intubation.

Infants have traditionally been described as "obligate nasal breathers" because of difficulty maintaining adequate ventilation when the nasal passageways are obstructed secondary to congenital anomalies (e.g., bilateral choanal atresia), with inflammation or infection of the airways, which produce mucosal edema or secretions, and after certain therapeutic maneuvers (e.g., placement of an NG tube). Of note, the nasal airway may account for as much as 50% of total airway resistance. An alternative descriptor, "preferential nasal breathers," has been proposed, since many neonates with obstructed nasal passages can transition to oral breathing, a process involving activation of the levator veli palatini and musculus uvulae [473]. Nonetheless, in the setting of nasal airway obstruction, oxygen desaturation may occur,

and—even after a successful transition to mouth breathing—respiratory failure due to fatigue may follow [474]. Of note, obstruction of the nose can exaggerate resistance to airflow and interfere with sucking–swallowing responses that may increase the risk for aspiration [475]. Airflow via the nose also offers a kind of "trophic" flow of sensory input so that interfering with this stimulation may impact olfactory development. The local effects in the development of structure and function of the upper airway may accompany nasal obstruction [475].

At all ages, the activities of the closely aligned structures of the upper airway (the tongue, pharynx, epiglottis) must integrate to allow coordinated eating/swallowing and breathing. The neonate faces unique challenges in coordinating these activities because sucking, swallowing, and breathing occur simultaneously so often. For example, the more cephalad location of the larynx forces the epiglottis adjacent to the soft palate facilitating nasal breathing during sucking. Over the first year, the infant converts to primarily oral from primarily nasal breathing, as the oral cavity enlarges and the larynx descends, as the neck elongates with growth.

The larynx of the neonate differs from that of children and adults. Based on observations of castings of cadaveric airways, the shape of the newborn larynx has been traditionally referred to as "funnel-shaped," becoming more cylindrical (i.e., adultlike) with growth. However, reports of in vivo imaging have noted that the neonatal larynx is cylindrical, similar to those of adults [476–478]. Also similar to adults, the glottic opening (true vocal cords) in sedated infants appears to be the narrowest part of the juvenile upper airway, but the cricoid remains *functionally* the narrowest part of the airway. The confusion may be attributed to the failure to gate the MRI to the respiratory phase when the glottis was filmed. While the circumferentially rigid ring of the cricoid cartilage is unyielding, the vocal cords can be opened gently, from the at-rest position, to accommodate rigid structures, like a tracheal tube [476]. In the neonate, the anterior larynx is more caudal than the posterior larynx, resulting in an elliptical shape to the inlet – narrower in the transverse plane than in the anterior–posterior dimension [477, 478]. Forcing a tight-fitting, circular tracheal tube through the subglottis can cause excessive pressure to the mucosa in the anterior–posterior axis, resulting in mucosal ischemia, subglottic edema, short- or long-term stridor, and airway scarring or stenosis [476].

Other characteristics of the neonatal airway must be considered during tracheal intubation [479]. The neonate's neck is relatively short and the larynx located more cephalad (C3–C4) (of note, the larynx is more superior, not more "anterior") compared with that in the adult (C4–C6). The narrow epiglottis may be omega- or U-shaped and difficult to elevate directly with a laryngoscope blade. The relatively large tongue, soft submandibular structures that are prone to compression by a ventilator's fingers or cricoid pressure, predisposes the neonate to upper airway obstruction. With less cartilage, smooth muscle, and contractile elements, the trachea is more compliant but with greater resistance to flow [480]. Because of a lack of development of the fascia that stabilizes the neck and immaturity of control of the upper airway muscles that stabilize the pharynx, the upper airway of the preterm infant is especially prone to collapse [481].

If the same volume of gas that passes through the narrow upper airway per unit time flows through the millions of alveoli in the distal lungs at the same time, then the gas flow in the upper airway must be very rapid or turbulent. In contrast, the slower flow of gas farther down the airways, from the fifth bronchial division to the alveoli, where the cross-sectional area has increased, becomes laminar. The airway resistance to flow, R, in the upper airways (where flow is turbulent) is inversely proportional to r^5. In contrast, the R in the lower airways where flow is laminar is described by Poiseuille's law: $R \propto (\eta L)/r^4$, where η is the viscosity, L is the length, and r is the radius of the airway. Although R is proportional to the length of the airway, it is exquisitely sensitive to changes in the radius of the airway, such that a small decrease in the radius markedly increases R to airflow. Notably, in the cricoid ring region of the upper airway, decreasing the radius of the airway by half (e.g., airway edema with infection or trauma) increases the baseline airway resistance to the fifth power or 3600% (increasing work of breathing dramatically, which can result in fatigue and respiratory failure in the preterm infant).

The lower airways are compliant and can readily collapse, increasing airway resistance, decreasing peak airflows, and increasing work of breathing. Wheezing may be audible but may or may not be associated with actual bronchospasm. Not surprising, since wheezing in the neonate is associated with many causes other than bronchospasm, response to bronchodilators is unpredictable [482].

Anatomy of Chest Wall and Mechanics of Breathing

The chest wall, which consists of the rib cage, abdomen (despite the term "*chest* wall"), and associated musculature, functions both as the respiratory pump and framework for the respiratory system. When compared with older children and adults, the respiratory pump is less efficient in the neonate due to anatomic, mechanical, and histologic factors [483]. The geometry of the pliable rib cage is more horizontal compared with the angulated structure in the adult, potentially limiting the outward and cephalad expansion of the thoracic cavity during inspiration [484] (Fig. 2.12). Finally, unlike the dome shape of the adult, the diaphragm of the neonate is flattened and inserts into the chest wall at an angle that results in a lower range of displacement.

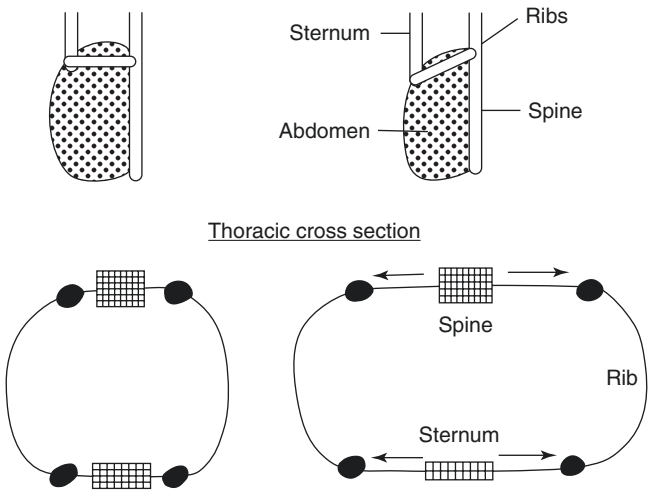

Fig. 2.12 Observed changes in configuration and cross-sectional shape of the thorax from infancy to early childhood. *Upper panel*: infantile and adult rib cage configurations. *Lower panel*: how rib growth at costochondral junctions and posterior rib angles could explain the observed changes in the cross-sectional shape of the thorax (from Openshaw et al. [484])

Resting lung volume (VR) results from the net effects of the outward elastic properties of the chest wall and the inward elastic properties of the lungs. With the inward elastance of the lungs being much greater than the outward elastance of the chest wall in neonates, the compliance of the cartilaginous chest wall (CCW) is much greater than that of the less pliable lungs (CL). Therefore, the properties of the less-compliant lungs primarily determine the overall compliance of the neonatal respiratory system (CRS) [485]. The CCW/CL ratio summarizes these relationships. The large CCW/CL ratio of the neonate signifies the dominance of inward forces [486–488] and, therefore, predicts small resting lung volumes [488].

Further, the compliant chest wall deforms inward during spontaneous inspiration, creating inefficient chest wall motion, significantly decreasing the mechanical efficiency of inspiration. Thus, distortion of the chest wall wastes energy [485, 489, 490]. As the chest wall matures and stiffens (contemporaneously with the onset of the demands of upright posture), C_{CW} decreases to approximately C_L [485], perhaps mediated through mineralization of the rib cage and/or increased chest wall muscle tone, as suggested by studies in lambs [487, 491].

The respiratory muscles change in conformation, molecular biology, and function during development. During gestation, trained by fetal breathing, the respiratory muscles can power respiration at the time of term birth, although with a limited reserve [492]. The respiratory pump in the neonate does not tolerate a large respiratory load compared with the adult, and thus, it is predisposed to failure [483, 484]. As with other muscle systems, the respiratory muscles, principally the diaphragm, can be characterized in terms of preload, afterload, and intrinsic properties of the fibers. The susceptibility of the neonatal diaphragm and intercostal muscles to respiratory fatigue often is logically attributed to the relative paucity of type I cells [493]. That is, type I muscle cells are characterized by slow cycling, aerobic metabolism, and resistance to fatigue and seem well suited for respiratory cycling. The preterm infant diaphragm may have less than 10% type I cells; by term, the proportion increases to ~25–30%, and through late infancy, the population of type I cells increases to the adult proportion of ~55% [493]. However, directly correlating these data to "fatigue" is controversial. Although the total cross-sectional area of all fiber types is small, some suggest that fatigue resistance is greater in the neonate compared with older infants [494]. That is, when other aspects of structure (e.g., myosin heavy-chain isoform [MHC] expression, MHC protein content) and specific function (e.g., maximum specific force, twitch contraction times) were considered, the neonatal diaphragm was regarded to be more resistant to fatigue [495].

Developmental expression of distinct myosin heavy-chain isoforms with less energy demands may protect the neonatal diaphragm from fatigue by decreasing energy demands [495, 496]. In a study of the diaphragm of the lamb over an extended developmental period (mid-gestation to 2 months postnatal), the susceptibility to fatigue decreased in late fetal life but reached its apex at approximately 1 week after full-term delivery, a finding that may be due to this experimental model of fatigue, in which maximal isometric contractions were induced in diaphragm isolates—contractions that are more forceful at term, such that the term diaphragm muscles were performing more work before becoming fatigued [497]. In the last two weeks before term, as fetal breathing became more regular and episodic, the specific force increased two-fold. The improved maximum specific force correlated with the increase in MHC content. Similar to earlier studies, the increase in MHC 1 content correlated with an increase in oxidative capacity. Alternately, the in vitro changes in resistance to fatigue must be considered along with the intrinsic properties of the developing diaphragm, including decreased diaphragmatic thickness and less effective force–frequency, length–tension, and force–velocity functions [498] that may increase the risk of respiratory failure [495].

The concept of susceptibility to diaphragmatic fatigue is complex, and in addition to the developmental effects on maturation, this muscle may be affected by the physiologic environment, including hormonal influence (e.g., cortisol, thyroid) and oxidative state (e.g., nutritional status, sepsis, acidosis). The respiratory pump may fail to produce sufficient work to maintain homeostasis, secondary to the intrinsic properties of the muscles of respiration or from unfavorable alterations in preload or afterload [499]. Conditions that affect intrinsic muscle function include metabolic derange-

ments (e.g., electrolyte disturbances), hypoxemia, shock [499], and maturation [500]. Hyper-expansion of the lungs due to air trapping alters preload. Inherent inefficient chest wall mechanics (see above), increased upper airway resistance (due to airway size and propensity to collapse), and changes in lung compliance due to respiratory distress syndrome, pulmonary edema, and other lung disease increase afterload (i.e., work of breathing). The central and peripheral nervous system components that control the respiratory pump can also contribute to respiratory failure (see Control of Respiration, below). Respiratory failure in the neonate can present with respiratory distress (e.g., tachypnea, retractions, use of accessory muscles), hypercapnia/respiratory acidosis, hypoxemia, and/or apnea. In addition to appropriate interventions (e.g., supplemental oxygen, mechanical ventilatory support including continuous positive airway pressure, nutrition), methylxanthines, such as caffeine (see Apnea of Prematurity), are sometimes introduced to improve diaphragmatic function [501, 502].

Consistent with the concept that infants with respiratory distress, especially preterm neonates, encounter a large "respiratory load" that is reflected in impaired muscle relaxation, experts have reported an index to clinically measure impairment of the respiratory muscles. That is, the time constant of respiratory muscle relaxation τ (tau) correlates with the risk for respiratory failure associated with muscular dysfunction [503]. For example, both maturity (gestational age) and infection directly affect τ. Similarly, these investigators applied this measurement to preterm infants whose airways were intubated during a trial of spontaneous breathing (SBT) to predict outcome after extubation. Infants with slower relaxation (larger τ) and larger τ at the end of the SBT compared with the value at the start [503] predictably failed extubation. On the other hand, infants who were successfully extubated had a reduced baseline τ that decreased during the SBT. The authors emphasize that predicting the infants who would be extubated successfully can be easily calculated using the systems routinely available on mechanical ventilators. Similarly, this index has been applied to define optimal CPAP in neonates with intubated airways [500]. But, even if this index were adopted as another routine criteria for extubation or to guide ventilatory management, these studies imply that, in addition to the other factors, impaired muscle relaxation may also predispose the neonate to respiratory failure.

Functional Residual Capacity

The quantity of gas remaining in the lungs in passive (i.e., with no activity of respiratory muscles) conditions is termed the functional residual capacity (FRC). The magnitude of the FRC results from the net effect of the competing forces of inward recoil of the lung and outward elasticity of the chest wall. In neonates, the transpulmonary (intrapleural) pressure at rest is 0 cmH_2O, compared with -5 cmH_2O in adults [504]. With a compliant chest wall, lung volumes at end expiration during tidal breathing in the neonate approach FRC, creating a significant risk of small airway collapse [505], atelectasis, ventilation–perfusion mismatch, and hypoxemia. To compensate and to preserve FRC dynamically, neonates adopt several strategies: shortening exhalation via rapid respiratory rates [506, 507], "laryngeal braking" (auto-PEEP mediated by the dynamic partial closure of the glottis) [492, 506], the tonic activity of intercostal muscles to stabilize the chest wall [492], and, when lung volumes are reduced, grunting [508].

Depending on these dynamic alterations of exhalation to expand the end-expiratory volume above FRC in the setting of limited respiratory reserve, the neonate is at risk for ventilatory failure from conditions that increase respiratory work or impair neural control of respiration, including general anesthesia (with or without neuromuscular blockade), rapid eye movement (REM) sleep [483, 509, 510], systemic infection, and shock. In addition to its effects on intercostal muscle function that contribute to paradoxical, inefficient respiratory movement, central nervous depression relaxes the muscles of the upper airway increasing airway resistance and respiratory work. Decreased FRC and the ensuing atelectasis inflict further demands on the diaphragm, as the reduced lung compliance increases the work of breathing, and energy is required to re-recruit alveoli [488]. By decreasing lung compliance, increasing airway resistance (e.g., from airway edema), and/or decreasing diaphragmatic function, acute lung disease exacerbates the effects of anesthesia, sleep, and common disorders (e.g., infection) and anomalies (e.g., pulmonary hypoplasia). Continuous airway distending pressure (e.g., CPAP) [511] will maintain FRC and mechanical efficiency during anesthesia and sleep in the setting of lung or other diseases, including prematurity. Positive pressure ventilation can maintain and restore FRC, especially with PEEP (see Chap. 6, Neonatal Ventilation). A technique rarely used today is the application of external negative extrathoracic pressure (-14 to -18 cmH_2O), which increases FRC in preterm neonates [512].

In the fetus, a closed larynx traps liquid in the lung and this applies pressure to expand the lungs, a stimulus for growth and development [513]. However, this scenario is irrelevant after birth. The complicated process of transitioning from fetal to extrauterine gas exchange demands a highly regulated sequence of liquid clearance and establishing the FRC. Although the volume of lung fluid immediately before birth approximates FRC, the amount of liquid in the lungs at birth varies, in part, depending on timing and mode of delivery (e.g., vaginal vs. cesarean section) [514]. Combining a compliant chest wall, high compression forces during late-

stage labor, and increased abdominal pressure (flexion of the trunk with vertex presentation), high intrathoracic pressure during vaginal birth contributes to clearance of airway fluids. However, this process is more complicated than the so-called vaginal squeeze [514, 515]. Documented with time-lapsed phase-contrast X-ray imaging during birth (rabbits), liquid moves into surrounding interstitium during inspiration, increasing the FRC with each breath in an amount equal to the volume of liquid exiting [514]. That is, hydrostatic pressure drives the clearance of liquid and simultaneously establishing the FRC [516]. By lung ultrasound in healthy neonates, aeration of the lung and at least partial clearance of liquid was documented during the first minutes after birth with complete liquid clearance typically achieved within the first 4 h after birth ([517]. Postnatally, the transepithelial pressure associated with inspiration continues to clear liquid and maintain FRC. However, various expiratory maneuvers (braking maneuvers, grunting, crying) contribute by restricting the loss of gas volume between breaths. Furthermore, after the FRC has been established, epithelial sodium channels function to prevent liquid from reentering the airway during expiration [518]. Finally, by effects on surface tension at air/liquid interfaces, surfactant plays a role in establishing FRC (see Surfactant).

Of relevance and critical to supportive care during resuscitation, FRC increased in a steplike pattern but only during inspiration [519, 520]. As a result, standards for resuscitation have been modified to emphasize the initial critical role of clearing liquid from the lung by applying inspiratory pressure [100, 520]. However, especially in the preterm infant, positive pressure ventilation (PPV) via a mask is challenging and often ineffective secondary to low tidal volumes (poor mask fit, airway obstruction, poor pulmonary compliance, nonsynchronous with spontaneous effort) or, at other times, injurious because of large tidal volumes produced with high pressure (may be more relevant via a tracheal tube) [519]. Of note, especially in the preterm infant, a closed larynx may contribute to the failure of PPV [521].

Recently, CPAP rather than PPV has been recommended as the optimal ventilatory support for the neonate, reflecting the hypothesis that stimulating and sustaining spontaneous ventilation avoids the injury to both lungs and brain, especially in the preterm infant. For example, PPV has been associated with initiating an inflammatory cascade, a common pathway for multiorgan injury [522]. Specifically, both the overall rate of intraventricular hemorrhage (IVH) and rate of severe IVH (27%) was greater (51%) in those ELBW infants treated with a large tidal volume (>6 mL/kg) compared with the rates (13%, 6%) in those who received <6 mL/kg [523]. However, guidelines for the ideal strategy in the delivery room (e.g., optimal pressure), delivery devices, and monitoring systems (e.g., end-tidal CO_2 as evidence of the degree of aeration) continue to evolve [519]. Finally, although some experts [514] recommend prolonged inspiratory times (sustained inspiration) to help clear fluid from the lungs in neonates and to avoid mechanical ventilation, the effectiveness of this intervention has not been definitively established [524, 525]. Furthermore, the duration of and the pressure for this maneuver have not been defined. After aerating the lungs, subsequent strategies should focus on gas exchange rather than the clearance of lung fluid.

Pulmonary Function Testing

Some techniques for pulmonary function testing (PFT) in adults have been adapted to neonates and young infants. Equipment to measure PFTs in neonates must address the smaller tidal volumes and dead space without sacrificing precision or increasing resistance to airflow. Additional challenges include the need to sedate the infants and a paucity of normal reference data as a function of age (Table 2.1) and for

Table 2.1 Typical values of lung function in healthy individuals (from [528])

Parameter	Preterm infant	Neonate	1 year	7 years	Adult
Body weight (kg)	1	3	10	25	70
Crown–heel length (cm)	35	50	75	120	175
Respiratory rate (min^{-1})	60	45	30	20	15
Tidal volume (mL)	7	21	70	180	500
Anatomic dead space (mL)	3	6	20	50	150
Maximal flow at FRC (mL s^{-1})	80	150	300	–	–
FRC (mL)	25	85	250	750	2100
Lung compliance (mL kPa^{-1})	15	50	150	500	2100
Airway resistance (kPa L^{-1} s)	8	4	1.5	0.4	0.2
Specific compliance (kPa^{-1})	0.6	0.6	0.6	0.7	0.8
Specific conductance (s^{-1} kPa^{-1})	5	2.9	2.7	2.7	2.3

Divide compliance and specific compliance by 10 to obtain values in cmH_2O, multiply resistance by 10 to obtain values as cmH_2O L^{-1} s; divide specific conductance by 10 to obtain values in s^{-1} cmH_2O^{-1}

various disease states. The techniques adapted to neonates and young infants include whole-body plethysmography, gas dilution, and occlusion techniques, esophageal manometry, weighted spirometry, and interrupter techniques (for reviews, see [526–529]). During studies of pulmonary function, tubes, such as nasogastric tubes, should be placed in the smaller nostril to permit maximum flow via the larger passageway [530].

Static volumes and capacities (e.g., FRC and tidal volume [V_t]) are generally similar to adult values when normalized for body mass. Anatomic dead space as a proportion of tidal volume is similar in the neonate and adult (i.e., about 25% of V_t). Although the additional dead space introduced by airway devices (e.g., LMA) may be negligible in the adult, this effect is more significant in the neonate, given their smaller anatomic dead space. Closing capacity in the infant (~35 mL/kg) can exceed FRC (~30 mL/kg), leading to airway closure.

Alveolar surface area (VA) is 2.8 m^2 at birth, increasing to 75 m^2 in adults. This increase is related linearly to the body surface area [531]. However, since the metabolic rate and consumption of oxygen (VO_2) per body mass is greater in the infant compared with the adult, the ratio of VA to VO_2 is reduced, increasing the infant's risk for impaired gas exchange, especially in the setting of underlying disorders that limit VA, such as pulmonary hypoplasia. Ventilation–perfusion (V–Q) mismatch (i.e., alveolar collapse leading to intrapulmonary shunting) commonly causes hypoxia and shunting that can be quantified by noting the difference between alveolar and arterial oxygen tension (which can also reflect diffusion failure).

V–Q mismatching is exaggerated in infants with lung disease [532]. Alveolar ventilation (V-dot A) in neonates (~136–168 mL/kg/min) is approximately 2–3 times that of adults (~60 mL/kg/min) [533–535] reflecting the greater metabolic demand for oxygen (VO_2) (6–10 mL/kg/min vs. ~3.5 mL/kg/min for the resting adult) and greater production of CO_2. Increased oxygen demand coupled with atelectasis and intrapulmonary shunting explains the rapid development of hypoxemia with apnea (within ~30 s) [536], a finding with significant implications during induction of anesthesia (e.g., rapid sequence induction in the presence of a "full stomach").

Minute ventilation increases with either a greater V_t or respiratory frequency (f) or both. For a given alveolar ventilation, the optimal f and V_t minimizes the expenditure of energy [537, 538]. Although V_t per body mass in the neonate approximates that of adults, the normal respiratory rate is greater in the neonate (30–60 breaths/min) compared with the adult (18–22 breaths/min). That is, the work of breathing to achieve adequate minute ventilation in the healthy neonate is minimized at this increased respiratory rate [504, 539, 540]. Despite this strategy, the neonate (especially the preterm infant) expends a larger portion of total body oxygen consumption on ventilation (i.e., the oxygen cost of breathing) than does the adult. This phenomenon is exaggerated in the setting of lung disease [541, 542].

In the neonate, large alveolar ventilation and constant FRC compared with adults lead to a smaller FRC "buffer" [543]. However, changes in inspiratory gas composition (e.g., oxygen, anesthetic gases) will be reflected in changes in the alveolar and plasma gas concentrations more rapidly.

Pulmonary Surfactant

Endogenous pulmonary surface-active agent, or "pulmonary surfactant," provides multidimensional functions in maintaining lung volumes and modulating innate host defenses. This foamy, bubble-producing substance is a complex aggregation of macromolecules that reduces alveolar surface tension, decreases the tendency of alveolar units to become atelectatic, and increases pulmonary compliance [544, 545]. Surfactant is an emulsion of lipids (~90%), proteins (~10%), and carbohydrates [546]. Although most lipids are phospholipids (PLs) including the phosphatidylcholines (PCs) such as dipalmitoylphosphatidylcholine (DPPC), which comprises 40–45% (by mass) of mammalian surfactant [547], surfactant also includes other phospholipids as well as unsaturated phosphatidylcholine, phosphatidylglycerol, cholesterol, and other neutral lipids [548]. A heterogeneous mixture of lipids is necessary to convey the necessary properties of rapid spreading over the alveolar (water phase) surface and resistance to compression [549]. A generation of synthetic surfactants have been developed and these agents may eventually replace the animal-derived preparations [550].

Type II pneumocytes serve several critical functions in alveoli. For example, these cells serve as the progenitors of type I pneumocytes (the major population of the alveolar epithelium) that repair the epithelium after injury. Type II pneumocytes also produce the lipid and proteins [399, 551] needed to produce surfactant that is stored within characteristic organelles termed lamellar bodies. Surfactant is then released as tubular myelin by merocrine secretion, in response to stimulation such as β-agonists or stretch of the lung, eventually forming a monolayer over the alveolar surface, reducing surface tension at the alveolar air–water interface [547]. Thus, the various configurations of surfactant exist (i.e., tubular myelin, droplets, and the monolayer film) each supporting specific functions including spreading throughout the alveoli, forming a monolayer, acting as reserve surfactant when the monolayer is disrupted (e.g., by oxidation), resisting compression during exhalation, and rapid reabsorption [552]. The local environment (such as the changing physical forces during the respiratory cycle and calcium concentration) and the composition of various phospholipids and surfactant-associated proteins (SPs) that compose a particular surfactant molecule [399, 547] influence the

phases of surfactant. Thus, a complex pathway of highly regulated recycling or degradation (by alveolar macrophages) has evolved to allow for the energy- and substrate-intensive activity of this critical molecule [399]. Approximately 85% of the components of surfactant are recycled via reuptake into type II pneumocytes [553–556].

At approximately 20 weeks' gestation, mechanical forces related to fetal breathing stimulate the expression of genes that code for the production of surfactant [557]. However, without medical intervention, the quantity of surfactant is reliably sufficient to support spontaneous ventilation only after 32 weeks' gestation. In some preterm infants (most commonly, <32 weeks' gestational age), inadequate surfactant production manifests as respiratory distress syndrome (see below). Concentrations of saturated phosphatidylcholine, phosphatidylglycerol, SP-A, and SP-B increase during gestation. The ratio of two components of surfactant (lecithin to sphingomyelin, the L:S ratio) in amniotic fluid estimates fetal lung maturity. This ratio provides prognostic information on the fetus' expected pulmonary status. An L:S ratio >2.0 is associated with a reduced risk of RDS, whereas a ratio <2.0 is associated with an increased risk of RDS [558].

Surface tension as modeled as a sphere is described by Laplace's law $P = 2\gamma/r$, where P is the intra-alveolar pressure or "collapse pressure" of the alveolus (i.e., the pressure necessary to counteract the contracting molecular forces produced at the air/fluid interface—the inward force acting to shorten the radius of the sphere, promoting collapse) [559]. This law states that the distending pressure is proportional to the surface tension (γ) and inversely related to the radius of the alveolus (r). During inspiration, alveolar radii generally increase due to forces generated by the respiratory pump, and therefore, collapse pressure tends to decrease. At the end of expiration, significant distending pressure would be needed to prevent alveolar collapse without the effects of surfactant. In films lining the alveolus, surfactant can produce large surface pressures, decreasing the contracting force of surface tension. When alveoli are large, the surfactant monolayer is spread thinly over the alveolus, and because of the large radius, the effect of surfactant is not critical [560]. When alveoli are small (e.g., during exhalation), surfactant is compressed, further reducing surface tension in the setting of a small radius. Thus, surfactant acts to buffer surface tension over a large range of alveolar sizes.

However, alveoli do not operate in isolation and, instead, are organized into groups of acini [561]. The lung parenchyma, including the alveoli themselves, directly influences adjacent airways through traction [562]. At large lung volumes, such as those induced by positive pressure ventilation, the alveolar surface area to lung volume ratio is independent of surface tension (dependent instead on tissue interactions) [563]. In this case, the beneficial effect of surfactant therapy may be masked by the artificially augmented lung volumes [547]. In the macro perspective, alveolar and airway collapse are counteracted by the outwardly acting elastic recoil of the lung and chest wall, as well as the active respiratory control mechanisms described above.

In addition to its role in decreasing surface tension at the air–liquid interface, surfactant functions in a variety of inflammatory and immune pathways. For example, lipopolysaccharide, interleukin-1, TNF-α, and prostaglandins (especially PGE_2) are released during chorioamnionitis. Being within the amniotic cavity, inflammatory molecules have access to the fetal airway (i.e., during fetal breathing movements) and are known to induce synthesis and release of surfactant. Of note, this may explain the lung maturity that often accompanies preterm birth associated with chorioamnionitis. At the same time, various components of surfactant modulate and suppress inflammatory events within alveoli. Finally, in normal pregnancies, surfactant proteins (SP-A and SP-D) have been reported to promote the onset of labor [564]. Thus, the interrelationship of surfactant secretion and onset of labor, in the setting of superimposed effects of inflammatory stimuli, creates a complex and unpredictable environment for the fetus.

Distinct functions have been identified for the surfactant proteins (SP-A, SP-B, SP-C, and SP-D) [565, 566]. That is, the small hydrophobic proteins SP-B and SP-C interact with the surfactant lipids to reduce surface tension and stabilize surfactant when exposed to the changing mechanical forces of the respiratory cycle [567]. With lipids, these two proteins are packaged with lamellar bodies that are then secreted into the alveoli. SP-A and SP-D are hydrophilic oligomers, members of the collectin family of host defense proteins, that play a role in the innate immune response to microbial challenge by binding microorganisms and modulating leukocyte functions such as chemotaxis, cytokine function, and phagocytosis. SP-A and SP-D include recognition domains that facilitate immune cell recognition that coat infectious agents to enhance phagocytosis. Not only important for the innate immune system of the lung, in mouse models, these proteins modulate alveolar macrophage activity. As the most abundant of the SPs, SP-A facilitates the formation of aqueous surfactant aggregates, including tubular myelin. SP-D is not directly involved in the biophysical properties of lung surfactant but may play a role in surfactant reuptake and recycling [546, 568].

Thus, although the proteins overlap in function, "each surfactant protein has distinct roles in surfactant homeostasis and/or innate defense. The defense activity involves facilitating alveolar macrophages in antibacterial activity and minimizing inflammation to impede injury such as fibrosis. The integration of seemly diverse biological processes that are critical for pulmonary homeostasis" allows close regulation of interrelated processes. For example, the genes governing homeostasis of surfactant share common transcription factor binding sites with several innate host defense proteins [569].

Hereditary defects in the structure or the metabolism cycle of surfactant can lead to fatal or chronic lung disease, such as protein alveolar proteinosis [399]. Mutations in the genes encoding SP-B (*SFTPB*), SP-C (*SRTPB-C*), or the surfactant lipid transporter protein (*ABCA3*) disrupt production and packaging of surfactant. Several distinct *SFTPB* mutations have been identified in infants with neonatal respiratory failure or diffuse interstitial lung disease in neonates or children (i.e., neonatal or congenital pulmonary alveolar proteinosis, infantile desquamative interstitial pneumonia, chronic pneumonitis of infancy, nonspecific interstitial pneumonia), as well as the usual interstitial pneumonia in older children and adolescents [551]. Some mutations in the gene encoding SP-C may present as chronic interstitial lung disease in older infants, children, and adults [551, 570]. Because mutations are recessive, infants who are deficient in SP-B may have a family history of perinatal respiratory failure. More uncommonly, less severe mutations affect the production of SP-B in infants with chronic lung disease. In general, without lung transplantation, *SFTPB*-related lung disease is fatal in the first months of life [551].

Mutations in *ABCA3* are the most common cause of hereditary respiratory failure in neonates. Mutations are associated with abnormal lipid transport and "processing" of SP-B and SP-C. Patients present with congenital pulmonary alveolar proteinosis or infantile diffuse interstitial proteinosis, both usually fatal without transplant. Thus, this mutation resembles those associated with *SFTPB* in terms of onset and clinical course. Rarely, *ABCA3* mutations are identified in older infants, children, and adolescents with chronic interstitial lung disease [551]. Finally, GM-CSF signaling plays a critical function in modulating alveolar macrophages in their role in uptake and catabolism of both surfactant lipids and proteins. Because mutations in GM-CSF impair alveolar macrophage differentiation, clearance of surfactant lipids and proteins may decrease. Pulmonary alveolar proteinosis associated with mutations in the GM-CSF receptors results from the accumulation of surfactant lipids and proteins.

Therapy with a surfactant has been extensively evaluated and shown to significantly decrease neonatal and infant mortality in preterm neonates with RDS [548]. Clinical trials to evaluate surfactant began in the 1960s, but its effectiveness as a treatment was established only after the introduction of "natural" preparations of the compound in the 1970s–1980s. Natural surfactants (lipid extractions that only contain SP-B and SP-C) for patient care are derived from bovine and porcine lungs [571, 572]. As well, multiple generations of synthetic surfactants have been developed, but mimicking the complexity of natural preparations has been challenging. More recently, third-generation synthetic surfactants with SP-B and SP-C as well as DPPC and palmitoyloleoylphosphatidylglycerol may offer more promise [550, 572]. If clinically effective, such agents may be more cost-effective.

Respiratory Distress Syndrome (RDS)

Neonatal respiratory distress syndrome (RDS), also known as hyaline membrane disease, results from insufficient surfactant production most often associated with prematurity but can occur when surfactant release or synthesis is delayed, as with infants of diabetic mothers, or with secondary inactivation of surfactant, as in meconium aspiration syndrome. In the setting of prematurity, the risk for RDS correlates inversely with gestational age with an incidence of approximately 5% in infants >34 weeks' gestational age, approximately 30% in those between 30 and 33 weeks, and at least 60% in those <28 weeks [566].

The clinical features of untreated RDS result from poor lung compliance, increased work of breathing, loss of FRC, V–Q mismatch, poor gas exchange, right-to-left shunting via the ductus arteriosus and/or patent foramen ovale, and lung injury from barotrauma and volutrauma, oxidative injury, and inflammation [573]. Neonates with RDS typically present with tachypnea or apnea, retractions, grunting, hypoxemia, and respiratory and metabolic acidosis. The typical appearance of RDS on the chest radiograph is a diffuse pattern of reticulogranular ("ground-glass") opacities and air bronchograms representing air-filled large airways surrounded by atelectatic alveoli [574]. Symptoms tend to worsen for several days after birth, followed by improved respiratory function as endogenous surfactant production increases. The infant with RDS is at risk of complications associated with positive pressure ventilation (e.g., chronic lung disease, pneumothorax, pneumonia), comorbidities (e.g., sepsis), and prematurity (e.g., injuries to other organ systems including the brain [see CNS]). Since effective surfactant function is critical to establishing a gas-filled FRC during the first few breaths after birth, RDS usually presents in the early postnatal period.

The beneficial effects to the fetal lung of antenatal delivery of corticosteroids to the mother was documented almost 50 years ago but has only been widely incorporated into standard practice over the last two decades. Treating the preterm fetus in utero by administering betamethasone to the mother accelerates the maturation of the lung and increases the production and release of surfactant [575]. The standard regimen consists of two doses of 12 mg of betamethasone given IM 24 hours apart or four doses of 6 mg of dexamethasone given IM 12 hours apart, within 7 days of delivery, for fetuses of 24–34 weeks' gestational age [576]. Of note, this longstanding regimen has been associated with reduced rates of neonatal death, RDS, intraventricular hemorrhage, necrotizing enterocolitis, duration of mechanical ventilation, and duration of oxygen therapy [577, 578].

In addition to routine delivery of antenatal steroids, the development of exogenous surfactant, either synthetic or derived from animals, has revolutionized the treatment and

outcome of RDS [571, 577], including the severity of associated pulmonary complications such as BPD. Commonly, transient hypoxemia may follow the bolus delivery of surfactant. Less often, delivery may obstruct the tracheal tube and result in pulmonary hemorrhage or inadvertent volutrauma (after compliance has improved) [566]. Guidelines have been revised repeatedly since surfactant was introduced into clinical care ([571, 579–583]. Currently, CPAP (no one modality for delivery has been identified as superior) is introduced early in the delivery room to avoid intubation and the potentially injurious effects of positive pressure ventilation without routinely administering surfactant.

In summary, the following represents the current approach to supportive care for the preterm neonate with increased risk for RDS:

- Initiating CPAP early with subsequent *selective surfactant administration* in extremely preterm infants (e.g., neonates <30 weeks' gestation requiring mechanical ventilation) results in reduced rates of BPD/death when compared with treatment with prophylactic surfactant therapy [581–583]. Thus, the American Academy of Pediatrics [581] and the European guidelines on surfactant administration [582] recommend stabilizing infants with CPAP and, only if necessary, administering surfactant as early rescue therapy, but preferably within 2–3 h after birth.
- Specifically, recent studies focused on the protocol of prophylactic surfactant treatment with prompt extubation (intubate–surfactant–extubate [INSURE]) did not identify a benefit of prophylactic surfactant with INSURE over CPAP. That is, using surfactant selectively versus prophylactically is associated with decreasing BPD and/or death.
- Antenatal corticosteroids are recommended for women with preterm labor at <34 weeks' gestation. Observational studies suggest that antenatal corticosteroids may decrease mortality in those <26 weeks' gestation. The optimal treatment provides an interval of more than 24 h and less than 7 days after the start of steroid treatment to birth.
- Although the safety and efficacy of repeating courses of antenatal steroids remain controversial, beneficial effects on lung function of the preterm infant have been reported [584].
- Thus, delivery of antenatal corticosteroids augments the beneficial effects of routine continuous positive airway pressure (CPAP) in the delivery room, also contributing to eliminating routine prophylactic surfactant therapy [548].

Recently, less invasive modes for the delivery of surfactant have been increasingly incorporated into clinical care to avoid even a short period of positive pressure ventilation [548, 572, 585–587]. For example, less invasive surfactant administration (LISA), includes placing a thin catheter into the trachea with the aid of Magill forceps under direct laryngoscopy. A similar procedure (minimally invasive surfactant therapy [MIST]) includes a rigid adult vascular catheter (e.g., 16-G Angiocath) to eliminate the need for Magill forceps [585]. An LMA can serve as a noninvasive tool to deliver surfactant. Recent meta-analyses combining the different trials with these methods document reduced incidence of BPD and/or death [572], but to date, the ideal strategy to deliver surfactant noninvasively has not been pinpointed.

Because of the undisputed critical role of inflammation in the pathogenesis of BPD, corticosteroids have been extensively explored in this setting. Recently, to avoid the toxicity of *systemic* delivery, *inhaled* steroids (beclomethasone, budesonide, fluticasone, flunisolide, and dexamethasone) have been reported to reduce the incidence of BPD [583, 588]. Some suggest that intratracheal delivery of steroids prevents BPD [449, 548, 583]. This strategy has not been adopted as a routine treatment. The relevance of postnatal *systemic* corticosteroids in managing or preventing BPD remains controversial, with Cochrane reviews recommending that adverse effects outweigh benefits, especially for dexamethasone (see Postnatal Development of the Lung) [443, 444]. However, a recent trial with low-dose hydrocortisone documented less BPD without neurodevelopmental insults at follow-up at 2 years [589, 590]. Outcomes were improved in the subset of those born at 24–25 weeks' gestation [591]. On the other hand, a recent report concluded that hydrocortisone delivered between 7 and 14 days did not improve the outcome of "death or BPS" at 36 weeks' postmenstrual age [592]. The relevance of *systemic* corticosteroids to the preterm infant, especially ELBW infants, continues to evolve, but in general, is reserved for those who remain dependent on mechanical ventilatory support after several weeks [444].

Despite advances in nursery care over the past several decades, approximately 20% of infants with RDS will develop chronic lung disease, specifically bronchopulmonary dysplasia (BPD), characterized by the persistent need for oxygen at 28 days of life [593], with grading BPD at 36 weeks' gestation (for infants born <32 weeks' gestation). Furthermore, the incidence of oxygen dependence at 36 weeks has not declined, and lung function in childhood has not improved over time [443]. Of long-term significance, pulmonary hypertension remains common and, at times, persistent in this population (see Postnatal Development of the Lung) [594].

BPD in the age of surfactant therapy differs from classic or "old" BPD, which was common in relatively mature preterm infants who had been subjected to high levels of positive pressure ventilation and oxygen therapy [595, 596]. Old BPD is characterized by alternating sites of hyperinflation (presumably areas of lung with normal compliance exposed to positive pressure ventilation) and atelectasis, extensive

fibrotic areas, and severe epithelial and endothelial lesions [597]. "New" BPD develops in infants treated with more current therapy for RDS (e.g., "gentle ventilation"), is most commonly seen in ELBW infants, and has pathologic findings that differ from those in "old" BPD, including enlarged, simplified alveoli, with some interstitial thickening [598]. New BPD appears to be a developmental disorder that results in disrupted lung growth associated with factors other than a deficiency of surfactant [599, 600]. Although neonates with new BPD may have a more benign pulmonary presentation in the ICN, many develop a non-asthmatic obstructive airway disease as infants or children, which has the potential to complicate ventilatory support, later anesthetic care, and the postoperative course [443, 595, 596, 601]. Although the long-term prognosis of new BPD has not been completely defined, the early disruption in normal lung growth and development may predispose to decreased respiratory reserve that may lie dormant until later life, becoming apparent when added to the expected decline in lung function associated with the aging process, smoking, or other respiratory insults [421, 423, 470, 601–605]. Finally, the impact of pulmonary hypertension contributes to the morbidity and mortality of BPD (see Postnatal Development of the Lung).

Oxygen Toxicity

Although an essential metabolic substrate for human life, oxygen can be toxic by creating reactive oxygen species (ROS) [606]. ROS act as second messengers and transcription factors important in growth and development, critical for immune function, and serving to regulate vascular beds including the ductus arteriosus [607]. For example, ROS modulate mitochondrial function, the expression of several stress proteins, and the production of regulatory T cells [608]. However, exposure to ROS can also be harmful, leading to the release of mitochondrial cytochrome C and other apoptotic factors, degrading signal transduction, directly altering proteins and impairing protein synthesis, modifying nucleic acids including injury to DNA bases and strands, and affecting cell growth and development. In the central nervous system, ROS seem to modulate aspects of "synaptic plasticity," but excessive exposure is associated with neurotoxicity [608]. Several mechanisms (thiol compounds such as thioredoxin and glutathione, uric acid, bilirubin, antioxyenzymes) maintain reduction–oxidation homeostasis [606, 607]. Other molecules (superoxide dismutase, catalase) serve to maintain the physiologic balance by scavenging excess ROS.

Eukaryotic life has evolved mechanisms to manage hypoxic but not hyperoxic environments, as the atmospheric concentration of oxygen throughout evolution has been similar to or less than the current concentration [609]. During normal development in utero, compared with postnatal life, the expected environment is one of physiologic hypoxia, extending from the nearly anoxic conditions of the zygote to late gestation when the PaO_2 reaches 20–30 mmHg. Embryonic stem cells grow and differentiate more efficiently at oxygen tension of ~10–15 mmHg (compared with 25 mmHg) [610]. Hence, despite the "hypoxic" milieu, growth and development continue at faster rates than at any other period in a lifetime.

Humans have evolved mechanisms to tightly regulate oxygen levels, at both the macro (carotid body reflexes) and cellular/mitochondrial levels [609]. Experts refer to HIF-1 as the "master regulator" of adaptive responses to hypoxia at the cellular level [610]. This protein complex governs a range of responses to hypoxia including the shift from aerobic to anaerobic metabolism [611, 612]. Specifically, in part via HIF-1, prolonged hypoxia elicits angiogenesis via regulation of growth factors such as vascular endothelial growth factors (VEGFs), erythropoietin, placental growth factor, and angiopoietins [610]. Thus, HIF-1 maintains a pervasive role in the activation of gene products important for angiogenesis, stem cell proliferation, and CNS and pulmonary alveolar development (via the closely related HIF-2α) [609]. Exposure to oxygen decreases HIF activity, affecting developmental signaling, and, in that way, impacting the unique growth trajectory of the preterm neonate developing ex utero [609]. Of relevance, at birth, the infant's oxygen tension rapidly increases. Of particular concern, even when the FIO_2 is maintained at 0.21, in the ELBW infant (23–26 weeks' gestation is a mid-gestation fetus), values for oxygen saturation exceed those in utero and may reach extreme levels at higher inspired oxygen concentrations. That is, the increase in the peripartum pO_2 occurs during a period of critical growth for the preterm infant which, as an in utero fetus, would have continued to develop in a "hypoxic" milieu.

The effect of oxygen on the pathogenesis of retinopathy of prematurity (ROP) has long been recognized since this disorder often is associated with obvious impaired visual acuity. Although factors other than hyperoxia contribute to both the development and severity of ROP, the role of oxygen has been linked to the effects of changes induced in VEGF and other growth factors in the developing retina. In addition to toxicity in the retina, potentially deleterious effects of oxygen have been noted in other organ systems after only a brief exposure (e.g., during neonatal resuscitation). In multiple systematic reviews, resuscitation with an F_IO_2 of 1.0 was associated with oxidative stress in animals [613–616] and humans [617]; neurologic injury in animals [618] and humans [619]; inflammation in the lung, heart, and brain in animals [620–622]; increased pulmonary vascular resistance/pulmonary hypertension in human neonates [623] and smooth muscle reactivity in animals [624]; kidney and

cardiac cellular injury in humans [625]; and increased neonatal mortality [619, 626, 627].

Neonatal resuscitation has changed radically over the past decade as international and national associations have revised guidelines to reflect the mounting evidence of toxicity associated with excessive oxygen administration. Currently, recognizing the critical role of establishing adequate ventilation in the transition to extrauterine life, pre-ductal pulse oximetry guides the delivery of supplemental oxygen to avoid hyperoxia [109, 628, 629]. For the first 5–10 min of life, the hemoglobin oxygen saturation of the healthy term neonate is frequently <90% (Fig. 2.13). Specifically, oxygen saturation in term neonates commonly increases to approximately 70%, 80%, 90%, and 95% at 1, 3, 5, and 10 min, respectively, after birth. For preterm neonates, oxygen saturation values are approximately 60%, 75%, 85%, and 95% at 1, 3, 5, and 10 min, respectively [630]. However, a recent report noted that preterm neonates who require respiratory support do not reliably increase oxygen saturation and heart rate as quickly as do spontaneously breathing preterm neonates who do not require respiratory support [631]. To establish rational clinical care, these patterns need to be clarified.

In response to identifying the toxicity associated with hyperoxia, initial ventilatory support for the term neonate should include an FIO_2 of 0.21. However, it has been suggested that "in newborns with severe circulatory arrest (Apgar <1 at 1 min), the HR response to the first ventilations even before obtaining a reliable reading from the pulse oximeter should determine the level of inspired O_2. When HR does not increase despite adequate ventilation, the inspired O_2 concentration should be rapidly increased" (even as high as an F_IO_2 of 1.0) to attain a rapid return of spontaneous circulation [633]. Recent updates remain consistent with these general recommendations [634–636].

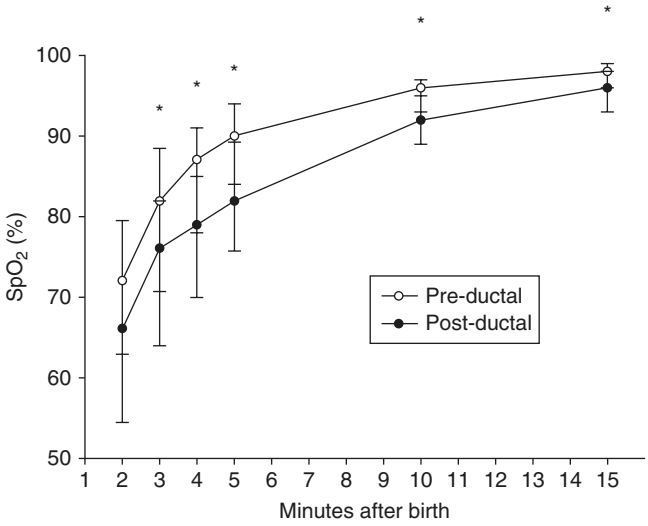

Fig. 2.13 Pre- and post-ductal SpO_2 levels in healthy term infants during the first 15 min after birth (median; IQR). Post-ductal SpO_2 levels were significantly less than pre-ductal SpO_2 levels at 3, 4, 5, 10, and 15 min. *$P \leq 0.05$. Pre-ductal SpO_2 measured on the right hand; post-ductal on one foot (from Mariani et al. [632] lung early SpO_2)

The incidence of ROP and lung injury in preterm neonates who receive supplemental oxygen titrated to oxygen saturations <93% are less than those whose oxygen saturation is maintained at saturations 95–98% [637, 638]. However, the recommendations for supplemental O_2 guided by pulse oximetry remain controversial for preterm neonates, especially for those who are extremely low birth weight. Although data from the Neonatal Oxygenation Prospective Meta-analysis (NeOProM) have been analyzed repeatedly and provide a preliminary framework for supplemental O_2 targets in this fragile group, definitive guidelines remain elusive.

The NeOProM collaboration included 4911 infants [639] across five separate, randomized, prospective, trials: the Benefits of Oxygen Saturation Targeting (BOOST) in New Zealand; BOOST II in the United Kingdom; BOOST II in Australia; the Surfactant, Positive Pressure, and Pulse Oximetry Randomized Trial (SUPPORT) in the United States; and the Canadian Oxygen Trial (COT) [639–642]. The infants in this study were <28 weeks' gestational age, enrolled within 24 h of birth, randomized to a target of a reduced (85–89%) or a greater (91–95%) range of oxygen saturation, and enrolled until 36 weeks' postmenstrual age. Although the protocols were designed to be consistent among the centers, differences in collecting additional secondary outcomes and the methods for assessing disability became apparent (e.g., Bayley Scales of Infant Development [BSID] II vs. BSID III). Interestingly, oxygen saturation frequently deviated outside of the two specified ranges and the distribution of oxygen saturation between the two groups overlapped. Finally, interpreting the results was complicated by an artifact in the calibration hardware (BOOST II and COT) that was identified during the active phase of data collection. This artifact exaggerated the difficulty of achieving compliance with the defined saturation targets and forced researchers to apply several analyses to the dataset. Experts continue to debate the optimal approach to analyze these data [643].

Nonetheless, experts have reached a moderate consensus on several aspects of these trials. Specifically, although no differences in the *primary composite outcome* (death or severe disability at 18–24 months of age) were identified, the outcome of the subset of "death" and the secondary outcome of NEC were greater and the incidence of severe ROP less in the group who were targeted to the lower range of oxygen saturation. Severe ROP that required treatment occurred more frequently in the group targeted for the higher SpO_2. Of concern, a recent letter noted, "this finding was inconsistent among studies, and a systematic review of 5 recent randomized trials (the NeOProM collaboration) rated the quality of evidence for this outcome as low" [644].

Also of concern, a study from Australia reported that the rate of severe ROP more than doubled after changing the target for oxygen saturation from 88–93% to 91–95% [645]. The concept of maintaining oxygen saturation within a specific range to reliably balance the risks and benefits remains challenging. As Cummings notes, "it is physiologically implausible for a single SpO_2 target range to be 'optimal' for all preterm infants, or even for a single preterm infant across the duration of an NICU stay. Neonates undergo dramatic developmental changes during the first weeks of life…significantly alter(ing) the physiology of the transfer of oxygen to tissue at any given SpO_2" [640]. In at least one study, the principle of setting the target for oxygen saturation based on gestational and postnatal age was associated with a smaller rate of severe ROP without increased mortality [646]. Finally, a recent analysis of a subset of patients in the SUPPORT cohort noted that SGA infants in the group targeting the lower range of oxygen saturation had the least median saturation and a greater incidence of intermittent hypoxemia (compared with AGA in the same group), which was associated with greater mortality [647]. The authors raise the topic of select susceptibility to oxygen toxicity in ELBW infants who are SGA, suggesting that saturation >92% might be appropriate in this subset.

The practical bedside exercise of maintaining a narrow range of oxygen saturation remains difficult and challenging. Although *targeting* an oxygen saturation between 85% and 89% may not be justified (based on data from NeOProM) and may result in episodes of severe hypoxemia, aggressively responding to a brief decrease to this range could result in repeated episodes of hyperoxia. Similarly, targeting an oxygen saturation of 95% may be associated with prolonged periods of "overshoot" and prolonged hyperoxia. The challenge of maintaining the oxygen saturation within a narrow range in the setting of unstable cardiorespiratory status at times is impossible, leading some to refer to oxygen targeting as "an illusion" [648]. That is, the sickest infants spend significant time outside the targeted range of oxygen saturation, resulting in significant periods of hypoxemia, hyperoxia, and/or wide fluctuations across a wide range of oxygen saturation [649]. Similarly, in a study that targeted oxygen saturations between 88% and 92% in preterm neonates with CPAP, compliance was achieved only 31% of the time. Infants encountered an average of 48 episodes of hyperoxia (SpO_2 >98%) and 9 of hypoxia (SpO_2 <80%). F_IO_2 was adjusted an average of 25 times per day [650]. Even in the setting of a prospective trial (NeOProM), the proportion of time outside the target range while on supplemental oxygen ranged from 8.2% to 27.4% (<85%) and 8.1% to 22.4% (>95%), with significant overlap between the groups [639]. Another expert reported that infants were only within the target range about 50% of the time [640].

Thus, the ideal oxygen saturation to target in the preterm neonate has not been authoritatively confirmed. Furthermore, some experts question whether oxygen tension or oxygen saturation provides a more reliable guide for oxygen saturation. For example, oxygen saturation of 85–95% in the first week of life represents a PO_2 of 29–67 mmHg [651]. The AAP Clinical Report concluded that "the ideal SpO_2 range for extremely low birth weight infants remains unknown" [652]. Some recommend setting the upper and lower saturation alarms to 95% and 89%, respectively [639], although the reliability of this recommendation is poor and maintaining compliance with a target rarely is possible for extended periods. The development of automated devices may offer more robust and reliable systems to avoid both hyperoxia and hypoxemia compared with manual control [653–655].

Control of Ventilation

A recent summary of the basic pathway for generating a regular, sustained breathing pattern includes the following framework (simplified). The so-called central pattern generator within the ventral brain stem produces the respiratory rhythm. That is, a group of interneurons in the medulla (the pre-Botzinger complex) initiates inspiration and then projects to various premotor inspiratory neurons within the ventral respiratory group. Finally, these neurons project to the motoneurons of the diaphragm and external intercostals as well as to upper airway muscles and the tongue [656]. Expiration is generated via a separate system within the brain stem. These respiratory-related neurons in the brain stem may regulate peripheral mechano- and chemoreceptors. Thus, the complex system for stable and responsive respiration requires a balance of excitatory and inhibitory input from higher brain centers, mechanoreceptors (lungs, upper airway), peripheral chemoreceptors (carotid body), central chemoreceptors (ventral medulla), and, finally the integrity of response from the diaphragm, chest wall, and upper airway. Input from the mechanoreceptor in the lung and the peripheral chemoreceptors has been reported to provide a greater regulatory role in the neonate compared with older infants [410].

In the setting of the preterm infant, immaturity at a variety of levels within this complicated and highly regulated network for controlling ventilation (the central nervous system, peripheral chemoreceptors, and target tissues [lung, larynx, respiratory muscles]) may interact to explain neonatal apnea and bradycardia [657] as well as postoperative apnea [658]. Although the regulation of respiration begins in fetal life, control matures significantly postnatally. For example, fetal breathing plays a critical role in lung growth and training of the respiratory pump (see Alveolar Phase), but in utero

this activity is not essential for gas exchange. Although some aspects of fetal respiratory behavior persist postnatally, the responses of the healthy term neonate to hypoxia and hypercarbia and other respiratory stimuli differ markedly from the rudimentary behavior of the fetus [659]. In early gestation, fetal breathing is continuous and under control of the spinal cord; as development progresses, fetal breathing is controlled more centrally and, by the third trimester, is a complex behavior that varies with the stage of sleep (e.g., in fetal lambs, breathing is impeded during non-REM sleep by inhibitory nuclei at the level of the brain stem) [659, 660]. In fetal sheep, hypercapnia stimulates and hypocapnia depresses the depth of fetal breathing [661–663]. Similar responses are present in the human fetus after 24 weeks' gestation, but at 24–26 weeks the response is less than after 28 weeks [664]. Thus, the fetus responds to the CO_2 tension qualitatively similar to the adult, although quantitative differences are apparent.

In contrast to adults, hypoxemia decreases fetal breathing. One hypothesis suggests that in the setting of limited access to oxygen, the fetus eliminates respiratory effort to decrease oxygen consumption when "breathing" does not contribute to gas exchange [659], but this is probably an overly simplistic analysis since the effect of hypoxia on fetal breathing is necessarily transitory as prolonged inhibition of fetal breathing would impair lung development [665]. Both decreased breathing and gasping are signs of fetal distress, are a component of the obstetrical "biophysical profile," and correlate with abnormal fetal well-being [666–668]. After delivery, inhibition of breathing movements is life-threatening and must be reversed as the neonate depends on pulmonary gas exchange for survival. The exact mechanism by which these pathways are reversed is unknown [659].

Although more mature than in utero, the neonate's responses to hypercapnia, hypoxemia, and afferent stimulation remain impaired, especially for preterm infants. The immature, central-chemoreceptor-mediated hypercapnic ventilatory response has a relatively flat slope in the neonatal period; with increased postnatal and gestational age, the slope increases toward adult values [669]. In animal studies, the immature ventilatory response to CO_2 is reflected in the failure to increase respiratory rate, although both immature and mature animals increase tidal volume in response to hypercarbia [670] (see Fig. 2.14). The origin of the diminished response to hypercapnia in the preterm infant has been attributed to dysfunction of the central nervous system [659]. However, preterm infants with a history of apnea exhibit a blunted ventilatory response curve to CO_2 with a slope that is even less than that exhibited by similar preterm infants without apnea [671–673].

The ventilatory response to hypoxia also is immature in the preterm infant. When hypoxic, preterm, and term infants less than 1 week of age initially increase minute ventilation for 1–2 min. Adults and term infants older than 2–3 weeks sustain this pattern. However, preterm neonates and term

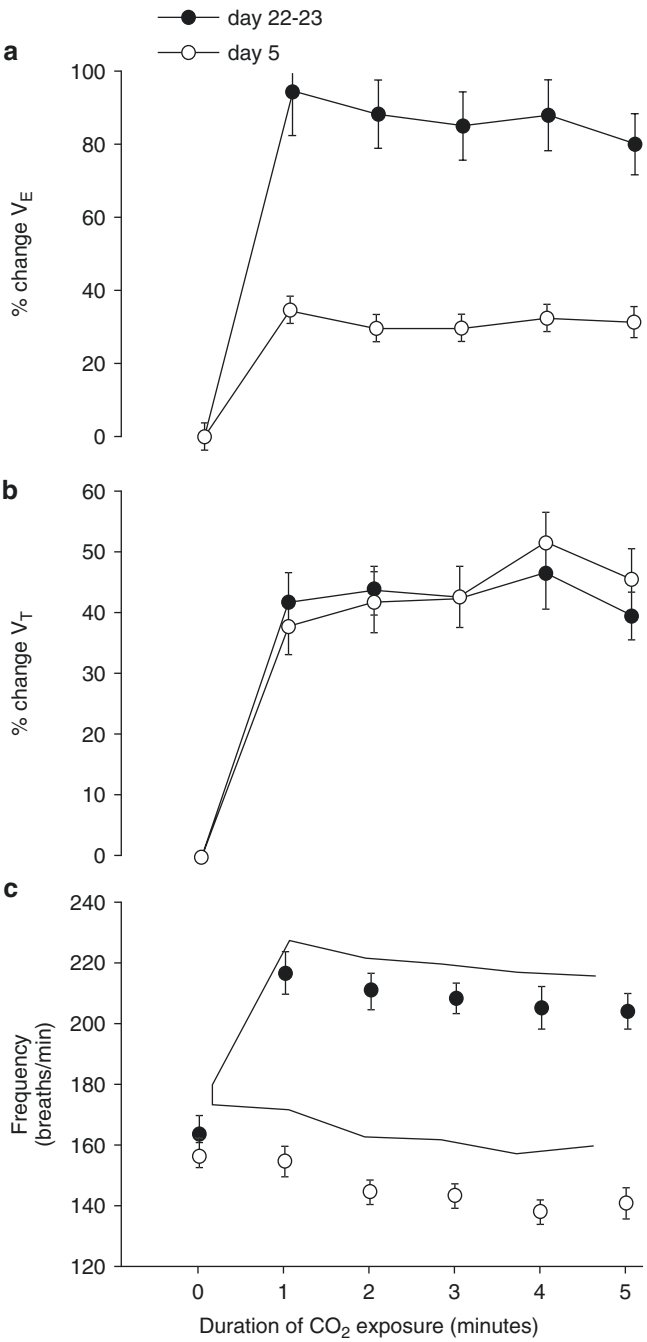

Fig. 2.14 Lung response to CO_2: effect of 5-min exposure to 5% CO_2 on $\dot{V}_E$ (**a**), tidal volume (V_T) (**b**), and frequency (**c**) at 5 and 22–23 days of age in unrestrained rats. Effect of 5-min exposure to 5% CO_2 on $\dot{V}_E$ (**a**), tidal volume (V_T) (**b**), and frequency (**c**) at 5 and 22–23 days of age in unrestrained rats. Values are means ± SE. Hypercapnia caused a significantly greater increase in $\dot{V}_E$ at 22–23 days compared with 5 days. Percent increase in V_T was similar at the two ages. Frequency decreased significantly from baseline at 5 days, whereas it increased significantly from baseline at 22–23 days (used with permission from Abu-Shaweesh et al. [670])

infants less than a week old exhibit a biphasic response to hypoxia. That is, the initial increase in ventilation (phase 1 or augmentation phase) is followed by a decline (phase 2 or depressive phase) to or below baseline; this phenomenon is termed "hypoxic ventilatory depression" (HVD) [659, 674–677]. Phase 1 is likely mediated by peripheral chemoreceptors located in the carotid body as denervation of these structures abolishes the reflex [675]. The initial response includes increased tidal volume and respiratory rate, followed by a gradual decrease in the respiratory rate. In the second phase of HVD in preterm infants, the increased tidal volume is preserved, but the respiratory rate decreases, resulting in a net decrease in minute ventilation [678]. In other species (sheep, rats, cats), the depressive phase is associated with a greater decrease in the tidal volume than the respiratory rate, but with more severe hypoxia, tidal volume may decrease as much or more than respiratory rate [676]. Across species, the augmentation phase is less in the early postnatal period compared with baseline minute ventilation, and the depressive phase declines with advancing postnatal age [676]. Thus, the magnitude of HVD correlates with the degree and duration of hypoxia and maturity.

The mechanism of HVD is not fully elucidated [676] but mechanisms within the central nervous system seem to be critical [679, 680]. For example, lesions in the pons diminish or abolish HVD in fetal lambs [681]. Other sites (medulla and midbrain) may also contribute [682]. Release of various neuromodulators also have been implicated in this central response to hypoxia, including adenosine, serotonin, prostaglandins [683], endorphins, GABA, platelet-derived growth factor, and an imbalance between neurokinin-1 and mu-opioid receptors, as pharmacologic modulation of these substances also resolves HVD [659, 684]. Depression of metabolic rate and changes in blood flow may also contribute [680]. Further support for the central origin of HVD includes the finding that in near-term infants, hypoxia shifts the CO_2 response curve to the right and decreases the slope (i.e., hypoxia blunts the CNS response to hypercapnia) [685]. In summary, the transition from a biphasic to a sustained hyperventilation in response to hypoxia is complex and may be related to increased activity of N-methyl-d-aspartate (NMDA) receptors (recruit excitatory signaling pathways that mediate sustained hyperventilation) and decreased input from platelet-derived growth factor (PDGF) (recruits signaling that reduce NMDA activity) [680]. Chronic exposure to hyperoxia (in rats) may also affect the development of the peripheral chemoreceptor response [683]. That is, after chronic hyperoxia during the first 2 weeks of postnatal life, return to a normoxia was associated hypoventilation primarily because of decreased sensitivity of the carotid body to hypercapnia and blunting of the hypoxic ventilatory response, but without phase 2 of this response. Carotid body sensitivity to CO_2 seemed to recover within 7 days after return to a normoxic environment. Of possible relevance to the preterm infant, chronic hyperoxia may impair the development of the normal response of the carotid body (not central chemoreceptors) to hypercapnia, implying a diminished capacity of this protective response. However, clinical relevance to the human has not been established.

The sensory neurons in the airway mediate the mechanical signals that have a critical role in the control of respiration. However, these reflexes mediated by afferents in the airway, lungs, and chest wall that regulate ventilation are immature in the preterm and young infant. For example, in preterm infants, mechanical or chemical stimulation of the larynx decreases ventilation and, in extreme cases, produces apnea [686]. Based on data from animals, the mechanism is associated with superior laryngeal nerve stimulation of inhibitory pathways leading to either decreased respiratory center activity or enhanced CNS inhibition/expiratory pathways [687, 688]. In part, the vagal receptor system mediates the complex process of establishing breathing during the transition from fetal to extrauterine life as well as maintaining effective ventilation in the neonatal period [689]. That is after denervation of the intrathoracic vagal nerve (newborn lambs), dysfunction of the surfactant system, and absence of vagally mediated volume input resulted in respiratory failure [690]. More recently, a molecular mechanism underlying the control of ventilation (in mice) at the level of airway sensory neurons has focused on the role of Piezo2, a mechanically activated ion channel. Newborn animals who lack this channel develop respiratory distress and die. Required to establish effective ventilation at birth as well as maintain normal breathing in adults, this channel serves as a "stretch sensor" that seems to have a role throughout life [691].

A respiratory control mechanism most relevant in the neonatal period, especially in preterm infants [692], the Hering–Breuer *inflation* reflex consists of inhibition of ventilation by lung *inflation,* is mediated by the slowly adapting pulmonary stretch receptors (SARs), disappears during REM sleep, and fades during the first few weeks of life. The Hering–Breuer reflex may stabilize ventilation even with changing elastic loads [693]. The strength of the reflex has been noted to increase during active (REM) compared with quiet sleep [694] and in the prone position [695]. In part, this may contribute to the reported improved oxygenation and pulmonary mechanics associated with this positioning.

A closely related phenomenon, the paradoxical reflex of Head, occurs when lung inflation triggers a large inspiratory effort resulting in a large lung volume and provides a rare example of a physiologic positive feedback mechanism. The reflex is accompanied by tonic inspiratory contractions [696, 697], which can be elicited in neonates via a forced inhalational maneuver with positive pressure [698], and is mediated by the rapidly adapting stretch receptors (RARs) (also responsible for so-called Hering–Breuer *deflation* reflex in

which rapid *deflation* of the lungs stimulates inspiration). The paradoxical reflex of Head may play a role in establishing the FRC during the transition from fetal life [698] and/or maintaining the lung volume in the setting of the compliant chest wall of the neonate [699].

Apnea of the Newborn

The immaturity of respiratory control (e.g., reduced sensitivity to CO_2 and hypoxia) and the mechanical properties of the respiratory system in the neonate (e.g., small airways, compliant chest wall) predispose to disorders of breathing, such as apnea. That is, immaturity of both the autonomic and central nervous systems as well as peripheral and central chemoreceptors fail to accurately regulate respiratory muscles and the upper airway. Finally, separate from imperfect neural input, a compliant chest wall and upper airway tend to collapse also leading to airway obstruction/apnea. Because of greater maturity of both the central nervous and respiratory systems, the term infant is physiologically equipped to adapt to postnatal life, Thus, apnea in the term infant should be considered pathologic and deserves a detailed evaluation to identify a specific etiology. For example, apnea in the term infant is more likely to imply a significant underlying condition such as brain disorders (e.g., hemorrhage, stroke, trauma, malformations, seizures, congenital central hypoventilation), metabolic instability (e.g., glucose, calcium, sodium, temperature), inherited errors in metabolism, lesions that predispose to airway obstruction (e.g., craniofacial anomalies, upper airway anomalies, masses/tumors), anemia, or infection. Although these pathologies also apply to and are relevant when evaluating the preterm infant, apnea of prematurity (AOP) deserves additional analysis.

One expert refers to apnea of prematurity (AOP) as a developmental disorder, since at birth, especially in the extremely low birth weight infant, the central and peripheral mechanisms for control of ventilation remain oriented to fetal life, when breathing is characterized by frequent pauses. These imperfect regulatory mechanisms coupled with the immature parenchyma and vascular bed of the lung in the setting of a compliant chest wall create the "perfect storm" for AOP [410].

The definition of apnea of prematurity varies, but commonly the disorder refers to a pause in breathing for greater than 20 s or shorter pauses accompanied by clinical evidence of hypoxia such as cyanosis or bradycardia [700, 701]. This well-accepted definition is not evidence-based [702] and a consensus statement for a clinically significant event based on the duration of a pause in respiration has not been developed [703]. For example, apneic events <20 s in duration can lead to clinical signs of hypoxia; conversely, apneic events up to 30 s may be observed in healthy term babies. Thus, the clinical consequences (desaturation and bradycardia) in the context of gestational/postnatal age rather than simply the duration of apnea may be more relevant to long-term risk and, in that context, contribute to developing guidelines for initiating and discontinuing treatment as well as monitoring after discharge from the intensive care nursery.

Apnea is classified according to the mechanism of dysfunction: *obstructive* (no airflow associated with respiratory effort; usually obstruction is at the pharyngeal level), *central* (no respiratory effort without obstruction), and—the most common—*mixed* apnea, with features of both obstruction and pauses in the respiratory effort [687]. The incidence of recurrent apnea increases as the gestational age decreases; 100% of infants <28 weeks' gestational age, 54% at 30–31 weeks, 15% at 32–34 weeks, and 7% at 34–35 weeks. By 40 weeks' postmenstrual age, 98% of infants no longer experience apnea [704]. Of note, apnea persists beyond 38 weeks' postmenstrual age more commonly in infants born at 24–26 weeks' gestation and in those who develop BPD. In most cases, episodes of severe apnea (requiring intervention) decrease in frequency earlier than less severe apnea (i.e., spontaneously resolves) [705].

Apnea may be accompanied by bradycardia (so-called As and Bs)—with or without hemoglobin desaturation, suggesting that a common pathway (e.g., vagal inhibition) may contribute to both phenomena [687]. With hemoglobin desaturation, direct carotid body effects may lead to further bradycardia; the net result is decreased oxygen delivery (Fig. 2.15). The common thread of inflammation/oxidative stress that characterizes the diverse abnormalities associated with prematurity (e.g., sepsis, intracerebral hemorrhage, anemia, patent ductus arteriosus, neurologic abnormalities, airway anomalies, and other systemic illness) has been proposed to play a modulating role in AOP. The chronic inter-

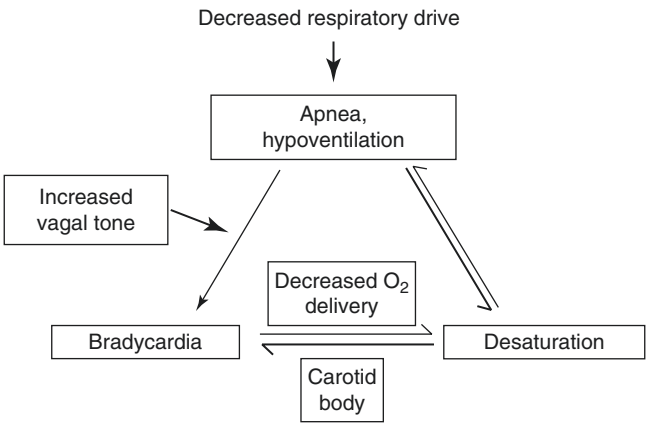

Fig. 2.15 A schematic representation of the sequence of events whereby apnea (or hypoventilation) results in various combinations of desaturation and bradycardia (from Martin and Abu-Shaweesh [687])

mittent hypoxia (CIH) that frequently accompanies AOP, not the respiratory pauses per se, has been linked to significant complications, including prolonged respiratory support, a greater incidence of ROP, delayed onset of oral feeds, and a greater risk for abnormal neurodevelopmental outcome [410, 706]. Infants with BPD have been reported to have a greater incidence of AOP [706]. Recently, systemic or local inflammation has been reported to upregulate inflammatory gene expression in the central nervous system (in the rat), inducing vagally mediated responses associated with apnea and CIH [410, 707]. Finally, recent studies suggest that epigenetic mechanisms (e.g., DNA methylation) associated with CIH in the newborn (rat) contribute to the altered sensitivity of the carotid body. Of significance, this neonatal "reprogramming" is associated with autonomic dysfunction in adulthood. For example, adults who encountered apnea of prematurity exhibit a greater incidence of sleep-disordered breathing [708, 709].

End expiratory lung volume (FRC) contributes to preventing prompt and severe desaturation in response to apnea. However, the compliant chest wall and pulmonary insufficiency commonly encountered by the preterm infant can decrease FRC. Activating chest wall muscles contributes to maintaining FRC by maintaining chest wall stability. However, the sleep pattern of preterm infants includes >80% in active sleep when chest wall muscle activity is inhibited [410], interfering with the stability of the FRC. Because the prone position stabilizes the chest wall (see Control of Ventilation), sleep in this position may stabilize FRC and, therefore oxygen saturation, especially in patients with BPD [410, 710]. As evidenced by the critical role of FRC in allowing oxygen uptake to continue in the setting of apnea (i.e., prevent/delay desaturation), the decrease in FRC during apnea has been shown to correlate inversely with the rate of desaturation. That is, the greater loss of FRC mirrors the rapidity of desaturation. Thus, the preterm infant is predisposed to a small FRC which increases the risk for severe desaturation in response to apnea [410]. Finally, titrating supplemental oxygen in extremely low birth weight infants to achieve oxygen saturation of 85–95% to avoid hyperoxia (see Oxygen Toxicity) may augment the risk for CIH in this fragile group.

In conjunction with nasal continuous positive airway pressure (4–6 cm H_2O), caffeine has evolved as the primary pharmacologic agent to treat apnea of prematurity. Although known to have a multitude of CNS effects, the role of caffeine (and other xanthines) in inhibiting adenosine receptors seems to be most relevant to treating apnea of prematurity. By blocking inhibitory A_1 and A_{2A} receptors, caffeine produces excitatory neural output, manifested clinically by increased minute ventilation, improved carbon dioxide sensitivity, decreased periodic breathing, and decreased hypoxic hypoventilation. Of note, hypoxic ventilatory depression (see Control of Ventilation) is thought to be mediated in the pons, with significant modulation via adenosine receptors.

Because of its long half-life, absence of side effects (tachycardia, dysrhythmias), and lack of need for monitoring with drug levels, caffeine has evolved as the preferred agent (usually, 20 mg/kg loading dose, 5–10 mg/kg/day maintenance). The Caffeine for Apnea of Prematurity (CAP) randomized controlled trial (and other studies) established a broad experience, defined a safety profile, and documented improved short-term outcomes (e.g., decreased duration of respiratory support, reduced frequency of BPD, less frequent use of corticosteroids, and increased survival without neurodevelopmental disability at 21 months). However, caffeine therapy did not significantly reduce the combined rate of academic, motor, and behavioral impairments at 5 and 11 years of age, but was associated with a reduced risk of motor impairment [711–713]. Despite these data, long-term cellular and molecular effects of caffeine on brain development in the setting of prematurity are unknown [714]. For example, gestational age and dose of caffeine may affect the balance of detrimental versus beneficial effects on the brain. Although some have advocated prophylactic dosing, especially in those <28 weeks' gestational age, the optimal timing for initiating therapy has not been identified [714, 715]. For infants >28 weeks' gestation not requiring ventilatory support, one approach is to initiate caffeine only if apnea develops [701].

A recent review and meta-analysis noted (observational studies, low quality of evidence) a significant benefit of early (less than 3 days of age) treatment in decreasing the risk for BPD [716]. Similarly, at follow-up at 11 years (CAP study), expiratory flow rates in those treated with caffeine were greater than in the control group. That is, the FVC was less than the fifth percentile in fewer children (11%) in the caffeine group compared with those in the placebo group (28%) [717]. Although some recommended larger doses of caffeine, no clear advantages for the larger dose have been identified [718]. Caffeine should be discontinued when the infant no longer demonstrates clinically significant apnea/bradycardia and is weaned from positive pressure for 5–7 days or at 33–34 weeks' PMA, whichever came first [701, 719].

AOP should be differentiated from other breathing patterns of the neonate. For example, periodic breathing is a common physiologic pattern that includes short pauses in respiration interspersed with high-frequency ventilation. This pattern has been attributed to discoordination in the feedback control mechanisms of the respiratory control center and generally resolves by one month of age in the term neonate [720, 721].

Apnea associated with anesthesia and surgery in the preterm, term, and ex-premature infant remains a controversial topic with "more questions than answers" [722]. During the past 30 years, little new evidence has emerged regard-

ing the optimal timing of surgery, anesthetic agents, and predictors for perioperative complications in ex-premature infants [723]. The "historical risk" for perioperative apnea in ex-preterm infants ranges from 5 to 49% [658, 724–726]. However, more recently, a randomized controlled trial reported the overall incidence of apnea (0–12 h) was similar in ex-premature infants less than 60 weeks' postconceptional age who underwent inguinal hernia repair under regional anesthesia (3%) compared with a group who received general anesthesia (4%). Of note, the incidence of early apnea (0–30 min) was greater in the general anesthesia group (3%) compared with the regional anesthesia group (1%) [727]. This study confirmed that, although the incidence is low, life-threatening apnea occurs in both the PACU and later. Finally, these data are consistent with a Cochrane review from 2003 that found insufficient evidence to recommend regional anesthetics in place of general anesthesia [728], despite hypotheses that regional and neuraxial anesthetics may obviate postoperative apnea [729] in the ex-premature.

Apnea secondary to anesthesia may be related to inhibition of central respiratory centers, decreased respiratory pump efficiency, and impaired V–Q matching. Factors that are associated with an increased risk for postoperative apnea include postconceptional and gestational age, history of apnea, anemia (commonly seen in the former preterm infant), neurologic disease (e.g., history of intraventricular hemorrhage), chronic lung disease, and an increased oxygen requirement [658, 729]. Postanesthetic apnea has been commonly evaluated in the setting of inguinal herniorrhaphy since inguinal hernias are more common in preterm infants and are commonly repaired before hospital discharge to avoid the risk of incarceration [724]. Recently, delaying surgical intervention to offset the risks for apnea as well as the surgical complications associated with early repair (e.g., recurrence, damage to adjacent structures such as the testis) has been proposed [722]. This author reports, "despite the frequency of inguinal hernia repair in preterm infants, this issue remains unstudied in a high-quality manner. A large, multicenter randomized trial is currently underway to address the effect of timing on the short-term and long-term safety and efficacy of IH repair in this population."

Although most experts have emphasized the critical relevance of gestational and postconceptional age in analyzing risk for perioperative risk, comorbidities also deserve scrutiny. For example, a recent study compared the incidence of postoperative apnea in infants <45 weeks' postconceptional age with those between 45 and 60 weeks. Consistent with recent reports, the overall risk of postoperative apnea was 2.5% but 4.7% in group <45 weeks' PCA. Consistent with other data, postconceptional age inflicts the most significant risk for perioperative cardiorespiratory complications; all infants who required tracheal intubation and mechanical ventilation were <45 weeks' PCA. However, of critical importance, a history of BPD and NEC also increased the risk. Specifically, in the absence of comorbidities, no patients in the older group encountered apnea [730].

Preventing postanesthetic apnea depends on identifying who should be monitored postoperatively, but these risks are not clearly defined. Some recommend that ex-premature infants <60 weeks' postconceptional age be monitored for respiration and hemodynamics after anesthesia until they are at least 12 h apnea-free (see [729] for proposed algorithms). Others suggest that those <46 weeks be observed for at least 12 h, with individualized care defined by associated comorbidities for those between 46 and 60 weeks [729]. These authors also recommend administering caffeine (10 mg/kg) IV. Others suggest overnight monitoring for patients born <37 weeks' gestation who are <50 weeks' PCA. Although the risks of gestational and PCA for perioperative apnea are well established, consensus for postoperative monitoring remains elusive.

Hepatic Function

Although the liver plays a critical role in fetal metabolism, the placenta and maternal liver manage a significant proportion of hepatic function in utero, providing a steady supply of glucose and other substrates. Throughout gestation, it is notable that the lower limit of glucose concentration is approximately 54 mg/dL [731]. In response to either hyperglycemia (e.g., infant of a diabetic mother) or hypoglycemia (e.g., intrauterine growth restriction), the fetus can induce or suppress hepatic glucose and/or insulin production. Although the enzymes for gluconeogenesis are present by the third month of gestation, gluconeogenesis is not active in the normal fetal liver. A variety of hepatic enzymes important for gluconeogenesis (e.g., glucose-6-phosphatase) develop rapidly after birth [732, 733]. In the immediate postnatal period, the neonatal liver must assume the same metabolic roles performed by the adult liver, a process largely completed within hours. Understanding the differences between fetal and neonatal versus adult hepatic physiology is a requisite for providing optimal care to the neonate.

Anatomy

The liver's unique architecture and cellular composition reflects its central role in metabolism and clearance, as well as hemostasis, hormonal regulation, and biosynthesis. In postnatal life, the liver has dual blood supplies. The hepatic artery provides richly oxygenated, arterial blood to the liver. The portal vein delivers a variety of substances from the digestive tract, including digested food products (e.g., free fatty acids, amino acids, glucose), as well as large proteins,

gut-derived hormones (e.g., glucagon), microorganisms, and immune cells and signaling molecules [734]. The canaliculi are a network of tubules, joined by tight junctions, that coalesce to form ducts, through which bile is actively secreted and, under positive pressure, flows from the biliary tree into the small intestines [735]. From mid-gestation, two types of epithelial cells populate the liver: hepatocytes and cholangiocytes (biliary epithelial cells). Hepatocytes are arranged in "cords" that are one cell thick with a basal domain adjacent to sinusoidal endothelial cells to exchange nutrients and metabolites with blood. The apical lumen includes the bile canaliculus, into which bile is secreted. Cholangiocytes establish a typical epithelial polar structure to form intrahepatic bile duct tubules to connect the bile canaliculi to the duodenum (via hepatic and common bile ducts) to drain bile secreted by hepatocytes. During this process, cholangiocytes adjust the composition of the bile (e.g., secrete chloride and bicarbonate and/or secrete or absorb water) [736]. On a macro scale, the hepatocytes are simultaneously in physical communication with the blood (hepatic artery/portal vein) and gut (canaliculi). These cells function as regulators of processes that span the gut, the bloodstream, and—in fetuses—the placenta. Disruption of these activities (e.g., with sepsis) can lead to cholestasis, hepatocyte injury, and giant cell hepatitis [734]. In their unique milieu, hepatocytes take on many critical physiologic functions including processing absorbed nutrients (glucose, amino acids, lipids); responding to gut hormones; clearing endogenous (e.g., damaged hemoglobin) and exogenous substances (e.g., drugs) from the blood, sometimes via the biliary tree; detoxifying bilirubin and ammonia; producing various serum proteins; and forming bile.

In Utero Development

The characteristic histologic features of the heterogeneous liver parenchyma—including sinusoids and canaliculi secured by tight junctions with hepatocytes straddling the spaces between—are formed by a set of complex processes, including apoptosis, morphogenic signaling, proliferation, and polarization of hepatocytes, involving cells from many embryologic tissue types [734]. At approximately the third to fourth week of gestation, the hepatic diverticulum arises from endodermal epithelia of the posterior foregut. These primitive pre-hepatocytes fold into mesodermal mesenchymal cells of the diaphragm forming a mixed population of cells of endodermal and mesodermal origin [737]. Under the control of a host of transcription factors, endodermal stem cells differentiate into progenitor cells which then are committed to becoming either bile ducts or hepatocytes [734, 738, 739], while mesodermal cells form blood vessels, Kupffer cells, sinusoidal endothelium, and fibrous, connective tissue. Meanwhile, the precursors of the hepatic and portal venous systems are formed from the yolk sack [740]. Populations of cholangiocytes further differentiate into the intrahepatic and extrahepatic portions of the biliary tree. A variety of transcription factors have been identified in the morphogenesis pathway of the biliary tree [736, 738, 739].

The common bile duct first appears as a connection between the hepatic bud and duodenum, and the gallbladder and cystic duct emerge as outgrowths. For the first three months of gestation, the extrahepatic bile ducts are occluded with endodermal cells. That is, biliary atresia, intrahepatic bile duct paucity, and autoimmune diseases, including primary biliary cirrhosis and primary sclerosing cholangitis, have been linked to a genetic abnormality affecting development and maintenance of the biliary system. Similarly, interrupting the formation of patent intrahepatic bile ducts also can present as liver failure during infancy. For example, biliary atresia can develop if these ducts do not recannulate, sometimes leading to liver failure as early as in the first months of postnatal life (see Biliary Atresia, below). Alagille syndrome is characterized by a paucity of intralobular bile ducts as well as cardiovascular, ocular, vascular, and vertebral anomalies [741]. A genetic association in Alagille syndrome involves Jag-1 and the NOTCH signaling pathway, which has been found to regulate the formation of intrahepatic ducts in mice [736, 742–745]. Disruption of other signaling pathways have been associated with a variety of hepatic disorders such as alpha-1 antitrypsin deficiency, cystic fibrosis, Gilbert's disease, Dubin–Johnson syndrome, and Zellweger syndrome [734].

In the human, bilirubin can be detected by approximately 14 weeks' gestational age. In contrast to postnatal life, the placenta removes most bilirubin in utero, with fetal hepatic–biliary pathways eliminating only a small amount (see Jaundice and Hyperbilirubinemia below). The human placenta permits bidirectional transit of unconjugated bilirubin [746]. In animal models, the placenta efficiently clears bilirubin from the umbilical artery [747] and the amniotic fluid [748].

Beginning at 5–6 weeks of gestation and through the second trimester, the liver enlarges 40-fold to assume the primary role of hematopoiesis [749]. In mid-gestation, the liver contains more hematopoietic cells than hepatocytes. Recently, the time course of hematopoiesis in the human liver was reported, confirming patterns of development and morphology similar to that documented in murine models and earlier studies in humans [750]. That is, although no clear hematopoiesis could be identified during the first 10 weeks, cells consistent with pluripotent hematopoietic stem cells (perhaps migrating from the yolk sac?) were localized in the lumen of sinusoids. Between 10 and 12 weeks' gestation, hematopoietic cells occupied roughly 20–30% of the hepatic parenchyma;

between 13 and 22 weeks, peak activity is associated with these cells occupying 70% of the parenchyma. In general, the erythropoietic lineage quantitatively dominates every stage, especially between 13 and 22 weeks' gestation. Later, between 23 and 39 weeks, cells of the erythropoietic line were at least three times greater than those of the myelomonocytic line. Finally, although present, megakaryopoiesis is a minor segment of the hematopoietic activity in the liver throughout gestation. Between 23 and 39 weeks, hematopoiesis involuted to occupy approximately 30% of the parenchyma. Thus, by the third trimester, the bone marrow emerges as the principal site of blood cell production, but extramedullary hematopoiesis continues in the liver until after birth [749].

By the end of the first month of human gestation, primitive hepatocyte function (protein synthesis and secretion) can be detected [751, 752]. In early fetal life, the major circulating protein is α-fetoprotein. At approximately two to three months of gestation, albumin synthesis can be detected, and adult serum concentrations are achieved by term. Glycogen synthesis starts by the tenth week of gestation, and by 12 weeks, bile is secreted at a rate approximately 50–60% of the level of adults [734].

Early Postnatal Hepatic Function: Anatomy

Throughout gestation, the fetus receives nutrients from the placenta via the umbilical vein, regulated by complex active and selective transport mechanisms for sugars, amino acids, fats, and molecules [753]. Before birth, the liver receives approximately 50% of umbilical venous blood, with the remainder shunting through the ductus venous to flow directly into the inferior vena cava and the right atrium. This shunt serves to stream oxygen-rich blood from the ductus venosus directly from the right atrium through the foramen ovale into the left-sided circulation and brain (Fig. 2.2). Hypoxia and reduced umbilical venous return induce a redistribution of flow away from the hepatic microcirculation to the ductus venosus and, therefore, to the left atrium (i.e., increased flow to the brain and other vital organs). Thus, the fetal liver plays a major role in determining venous return to the heart and in regulating the distribution of oxygen and energy substrates [754]. The liver receives variable amounts of the oxygen-rich blood flow, with most of the blood flow directed to the left lobe. Fifty percent of the blood flow to the right lobe arises from the umbilical vein and the remaining 50% from the portal circulation [755] (Fig. 2.3). As the percent of umbilical flow shunted through the ductus venosus decreases as gestation advances (i.e., 40% at 20 weeks to 15% at term), the percent of flow to the liver increases (i.e., 50% at 20 weeks to 85% at term), primarily to the right lobe [756].

When the umbilical cord is clamped, the liver no longer receives nutrient and oxygen-rich blood from the placenta. Instead, the portal vein becomes the primary source for nutrients from the gut, and the hepatic artery provides arterial blood with significantly greater oxygen content. After meals, the portal venous flow increases, providing twice the blood flow of the hepatic artery. The ductus venosus functionally closes over the first two postnatal weeks [757]. The neonatal liver comprises 4% of the body weight compared with only 2% in the adult, reflecting its critical function during this period [734]. Consistent with this, 25% of the cardiac output in the neonate is directed to the liver.

Early Postnatal Hepatic Function: Synthesis

Throughout gestation, the normal lower limit of glucose concentration is approximately 54 mg/dL [731]. However, without a continuous supply of maternal substrates from the umbilical vein, the newborn must maintain glucose homeostasis from sources of digested food, glycogenolysis, and gluconeogenesis. Until feeding is established, glycogen that has been stored mainly in the liver and heart during the third trimester breaks down into glucose under the control of two hormones: glucagon and catecholamines. Stress during delivery or as a result of illness can accelerate the depletion of glycogen stores, which may lead to hypoglycemia. Of note, deprived of glycogen that is synthesized and stored during late gestation, preterm infants are particularly predisposed to hypoglycemia. Also, primarily secondary to greater metabolic requirements from the brain [758], glucose consumption per body mass is greater in the preterm infant compared with the term. Similarly, small- and large-for-gestational age neonates incur greater risks for hypoglycemia, secondary to decreased stores (SGA), and unreliable glucose metabolism. Although key enzymes are expressed in the fetus, gluconeogenesis may not be active during fetal life. However, within 4–6 h of birth, gluconeogenesis plays an important role in glucose homeostasis [733] even in preterm infants [759].

Neonates who cannot tolerate adequate enteral caloric substrates must receive exogenous glucose support, often intravenously, to prevent hypoglycemia (see Chap. 8). Setting guidelines to evaluate and treat "hypoglycemia" has been challenging. For example, based on a mathematical analysis, a level >47 mg/dL was posited as a necessary threshold to prevent adverse neurologic events [760]. Despite emphasizing that confounding factors prohibited establishing a definite causal relationship, this number (<47 mg/dL) remains the commonly quoted threshold of neonatal hypoglycemia [731]. However, 47 mg/dL is not a "magic" number for treating neonatal hypoglycemia [761]. Because of conflicting data, experts admitted that: "We are not much closer today

to understanding the long-term neurodevelopmental consequence of hypoglycemia for these patients, and at what glucose concentrations to become concerned" [762]. Similarly, Adamkin recently acknowledged, "A consistent definition for neonatal hypoglycemia in the first 48 h of life continues to elude us" [763].

Because clinically managing hypoglycemia must include the context (e.g., persistently low level in an asymptomatic infant versus a single low value in a high-risk infant, such as an infant of a diabetic mother or SGA infant), the American Academy of Pediatrics has established somewhat complex guidelines for high- versus low-risk infants in the first 24 h of life, focusing on <4 h (25–40 mg/dL) and 4–24 h (35–45 mg/dL) after birth [764]. If a neonate requires intravenous glucose, the goal is to maintain the blood level >45 mg/dL. In contrast to the American Academy of Pediatrics, the guidelines from the Pediatric Endocrine Society focus more on hypoglycemia beyond the immediate neonatal period and recommend mean glucose levels of 55–65 mg/dL during the first 48 h after birth. The levels should increase so that by 72–96 h, the value should approximate those of older children and adults (>70 mg/dL).

Because blood glucose concentrations as low as 30 mg/dL are common in normal neonates at 1–2 h, are usually transient, and are characteristic of mammalian adaptation from intrauterine to extrauterine life, some authors classify this as "physiologic glucose homeostasis" [765]. Because of the variability in blood glucose levels over the first 3 days, based on a meta-analysis of published reports, some have defined "normal" glucose levels in *normal term* infants as a function of narrow ranges of postnatal age. That is, at 1 to 2, 3 to 23, 24 to 47, and 48 to 72 h of age, the lower threshold (<5th percentile) was reported as 28, 40, 41, and 48 mg/dL, respectively [766].

In summary, the AAP guidelines should be followed when managing high-risk symptomatic infants during the first 24 postnatal hours [767]. For infants between 24 and 48 h of age, the concentration of glucose should be maintained at >45 mg/dL. No evidence exists to modify these guidelines for infants undergoing surgery and anesthesia, especially if glucose monitoring is available intraoperatively.

The term as well as the preterm neonate responds to increased concentrations of circulating glucose by releasing insulin, which promotes the uptake of glucose either for immediate energy or for storage (as triglycerides or glycogen). Of importance, abruptly decreasing or discontinuing an exogenous source of glucose (e.g., discontinuing intravenous alimentation, separation from the placental delivery of high glucose concentrations during gestational diabetes, prolonged *NPO* period without an intravenous source of glucose) increases the risk for hypoglycemia. Other risk factors for hypoglycemia include liver dysfunction (e.g., shock or sepsis) and inborn errors of metabolism.

Amino acids via the portal circulation and plasma proteins via the hepatic artery are transported to the liver either to be degraded via the urea cycle or to serve as a substrate for liver-derived plasma proteins. These liver-derived proteins include most circulating proteins with the major exception of immunoglobulin [734]. Malnutrition or liver disease may be manifested by reduced concentrations of circulating proteins (e.g., albumin or ceruloplasmin). Conversely, acute inflammation decreases the efficiency of hepatic update and metabolism of proteins that lead to increased concentrations of certain circulating proteins (e.g., fibrinogen, an *acute phase reactant*). Healthy preterm infants often have a relative hypoalbuminemia, which results from decreased amino acid intake or albumin losses (renal, gut, or increased permeability [*third spacing*]), rather than an inability of the liver to synthesize large amounts of albumin [753]. Abnormal hypoalbuminemia can lead to or result from edema (i.e., *third spacing*), ascites, and congestive heart failure.

After a meal (or during parenteral nutrition), the hepatocytes regulate the metabolism of free fatty acids allowing their deposition as triglycerides in the liver or as adipose tissue. During fasting, these energy-rich molecules are converted to ketones and used for energy by neurons and other cells. A lack of ketone production is associated with a potentially fatal defect in metabolic pathways (e.g., deficiency of *long-chain 3-hydroxyacyl dehydrogenase*, an enzyme important in fat oxidation) [768, 769].

Early Postnatal Hepatic Function: Metabolism

The bile transport enzymatic system is activated when the liver transitions to the primary organ for bile elimination. Bile includes bilirubin (the end product of heme degradation) and the detergent-like bile acids (amphipathic sterol molecules synthesized from cholesterol). In addition to serving as important molecular building blocks for a variety of synthetic pathways, bile acids play an essential role in lipid digestion by emulsifying partially digested fat droplets, adsorbing lipid-soluble vitamins (A, D, E, and K), and activating key endogenous digestive enzymes as well as breast milk lipase (also known as bile salt-stimulated lipase) [770].

The enterohepatic circulation provides a critical mechanism for conserving bile. Approximately 95% of bile acids secreted into the intestine are reabsorbed via the portal venous circulation and taken up by hepatocytes via several specific bile acid transporter proteins [771]. Although bile acid production may be detected as early as 14 weeks of gestation [772], production is immature in the neonate, especially the preterm infant, increasing the risk for bile-deficiency-associated steatorrhea ("diarrhea of infancy"),

vitamin deficiency, and caloric malnutrition (see Jaundice and Hyperbilirubinemia, below).

After birth, hepatic enzyme activity increases rapidly. For example, while levels in cord blood [773] and in neonates are normally increased (mean values, 3.8–4.6 mmol/L) [774, 775], the concentration of lactate typically decreases to near-adult values within 24 h postnatally (mean 2.08 vs. 1.8 upper limit adult norm) [775]. Persistently increased serum lactate concentrations suggest increased production (poor perfusion and anaerobic metabolism), hepatic dysfunction, or mitochondrial metabolic defect [776].

In part, the variability in drug disposition in the neonate can be attributed to the maturation of drug-metabolizing systems and membrane transporter proteins. The ontogeny of these proteins is classified into three groups: high expression during gestation with low to no expression after 1 year of age (e.g., phase I metabolizing enzymes such as CYP3A7 and phase II metabolizing enzymes, sulfotransferase), stable expression of the protein (e.g., CYP3A5 and SULT1A1), and low expression during gestation but increasing postnatally [777]. The third category is probably the most common pattern, including enzymes such as CYP1A2, CYP2C19, CYP2E1, and CYP3A4 [777].

A tremendous effort has focused on establishing the patterns of development in the hepatic drug-metabolizing enzymes (phase I [oxidation–reduction reactions and hydrolysis], phase II [conjugation with glucuronic acid and other substances], and phase III [excretion from the liver/biliary system] reactions) critical for biotransformation and detoxification of exogenous substances and xenobiotics (e.g., medications) [777–779] (see Chap. 3). In contrast, the critical role of drug transporters has only recently emerged and remains in the early stages of investigation [780, 781]. A recent report focused on the organic anion transporters that function in the uptake of a wide range of molecules into a variety of organs, including the liver (e.g., OATP1B1 and OATP1B3). Substrates for these two transporters of the OATP family include bile salts, thyroid hormone, and methotrexate and angiotensin II receptor antagonists [782].

The cytochrome P450 system mediates phase I reactions and is variably induced at birth [783]. In addition to the enormous variability in developmental expression of these proteins, genetic (e.g., sex, polymorphisms) and nongenetic host (e.g., age, disease) and environmental factors (e.g., drug exposure) combine so that "every individual possesses his/her own unique CYP profile with important implication for drug treatment" [784]. Of particular relevance to the anesthesiologist are the drug-metabolizing CYPs (CYP1, A1/A2; CYP2, A6/B6/C8/C9/C19/D6/E1/J2; CYP3, A4/A5) that account for >95% of drug metabolism in adults [784]. Of importance, the genes that regulate the production of these proteins undergo developmental expression [777, 778, 785–787]. For example, although highly functional in utero, the activity of CYP3A7 rapidly diminishes by birth. In contrast, CYP3A4 is expressed minimally in utero, whereas by six months of age, activity increases to approximately 50% of adult levels [777]. Phase II reactions also follow age-related patterns. For example, glucuronidation (UGT2B7) of morphine does not reach adult rates until 2–6 months of age [787]. Another example includes human hepatic UGT2B15 that is expressed only late in gestation and maturation continues postnatally [788].

The immaturity of these pathways is associated with two clinically significant phenomena. First, the developing liver may be exposed to the toxic effects of large concentrations of compounds that cannot be excreted [789]. Second, to avoid side effects of high serum concentrations, age-related dosing may be required for drugs that are inefficiently cleared by the immature liver (e.g., certain muscle relaxants and opioids [790–793], midazolam [794], caffeine and theophylline [795], and propofol [796]). Finally, variability in CYP2D6, which is responsible for the metabolism of as many as 25% of commonly used drugs (e.g. antiemetics, β-blockers, opioids) has prompted classifying individuals as ultra-, extensive, intermediate, and poor metabolizers [797].

Early Postnatal Hepatic Function: Common Neonatal Hepatic Disorders and Hemorrhagic Disease of the Newborn

At birth, the liver rapidly increases the production of circulating proteins of the coagulation cascade (except factor VIII, which achieves adult levels within a few days). Although synthesized in the hepatocytes, the vitamin K (*koagulation*) carboxylation-dependent factors (II, VII, IX, and X) depend on the maturation of the digestive system to achieve normal function. The bacteria that colonize the gut after initiation of enteral feeds are an important source of vitamin K. Until the microflora are mature and the absorption of fat-soluble vitamins is robust, quantities of vitamin K may be insufficient to prevent pathologic bleeding (e.g., intracranial hemorrhage) [798]. For this reason, current guidelines (in the United States) recommend that healthy neonates receive 0.5–1 mg of parenteral (intramuscular) vitamin K shortly after birth, which significantly decreases the risk of both early and late bleeding secondary to vitamin K deficiency [799]. Otherwise, healthy infants do not require further supplementation, and vitamin K deficiency after 6 weeks is rare [734] in the absence of conditions that

impact its synthesis (such as antibiotic therapy affecting gut flora) or absorption of fat-soluble vitamins (such as liver disease, including hepatitis and alpha-1-antitrypsin deficiency) [800, 801].

Early Postnatal Hepatic Function: Common Neonatal Hepatic Disorders, Jaundice, and Hyperbilirubinemia

Neonatal jaundice refers to the easily visible cutaneous yellow-orange color that accompanies excess bilirubin deposits in the skin (total serum bilirubin levels >~5 mg/dL [85 micromol/L]) [802]. Increased serum concentrations of unconjugated bilirubin (which indirectly reacts with diazo reagents in the laboratory and, therefore, termed *indirect*) that is visually detectable occurs in approximately 65% [803] to 85% [804] of all normal infants during the first week of life as a normal and transient phenomenon. Cephalocaudal progression of jaundice is associated with, but is not a reliable measure of, absolute bilirubin levels. For example, when the bilirubin concentrations are approximately 5 mg/dL, jaundice is generally most apparent in the face, but as the serum concentrations increase, jaundice appears in the skin of the thorax and abdomen, but in a quantitatively unpredictable manner. Without jaundice, pathologically increased concentrations of bilirubin can be excluded [805, 806].

The so-called physiologic jaundice of the newborn (generally less than 12 mg/dL) results from the normal hepatic immaturity during the transition from fetal to extrauterine life. Of primary significance, because of two inherent characteristics of fetal hemoglobin, neonates encounter a large burden of bilirubin. That is, a relatively large red blood cell (RBC) mass coupled with a shortened erythrocyte life associated with fetal hemoglobin predisposes the newborn to hyperbilirubinemia. Further, the large quantity of bilirubin stored in meconium may be reabsorbed into the portal circulation (i.e., enterohepatic circulation) and hepatocytes, especially if elimination of stool is limited secondary to intestinal anomalies (e.g., bowel atresia and/or obstruction) or dysfunction (e.g., ileus with sepsis or necrotizing enterocolitis) [807, 808]. Jaundice should be considered abnormal if it [804]:

- Presents in the first 36 h of life
- Persists beyond 10 days of life
- Increases to >12 mg/dL
- Includes direct (conjugated) bilirubin >2 mg/dL and >30% of total bilirubin

Finally, immature processes in the liver contribute to the substantial risk for neonatal indirect hyperbilirubinemia. Uptake of bilirubin into hepatocytes for conjugation requires glucuronic acid and the organic anion transporter (OATP2) [809]. Furthermore, uptake into the liver is less efficient, in part due to low levels of ligandin, a hepatocyte cytosol binding protein [810]. Glutathione S-transferase contributes to the intracellular binding of bilirubin. Although low at birth, concentrations of this enzyme reach adult levels 1–2 weeks after birth. In the hepatocyte, lipophilic bilirubin is transformed into a polar, water-soluble substance that is suitable for excretion in urine (conjugated or *direct* bilirubin) by conjugation with one or two glucuronic acid molecules, a reaction catalyzed by uridine 5′-diphosphate glucuronosyltransferase 1 (UGT1A1). The activity of this enzyme is diminished in neonates, increasing to adult levels postnatally [811]. That is, the expression of isoenzymes of UGT1A1 is developmentally regulated; activity is 0.1% of adult levels at 17–30 weeks of gestation and 1% of adult values between 30 and 40 weeks of gestation, and adult levels are attained by 14 weeks of postnatal life. Unconjugated bilirubin induces hepatic UGT1A1 activity, independent of the gestational age [812].

The sterile gut of the neonate lacks the bacteria-mediated conversion of bilirubin to urobilinogen. As a result, conjugated bilirubin remains in the lumen, where it can be de-conjugated, in a reaction catalyzed by the enzyme β-glucuronidase. This unconjugated bilirubin can be reabsorbed via the enterohepatic circulation, further decreasing the efficiency of bilirubin excretion.

The enterohepatic system in the neonate should "catch up" with the increased load of bilirubin and decreased clearance within the first 2 postnatal weeks so that bilirubin concentrations can decrease to adult values by that time. Differentiating physiologic from pathologic concentrations of bilirubin presents a challenge as the range of "normal" varies among racial groups, with breastfeeding versus bottle-feeding, and other epidemiologic factors. Bilirubin concentrations are dynamic, and an absolute blood concentration that differentiates physiologic from pathologic is difficult to pinpoint [813]. Mechanisms for the production of and a differential diagnosis of neonatal hyperbilirubinemia vary from anatomic, metabolic, and genetic etiologies to exaggerated normal physiology (Table 2.2). Because the placenta efficiently clears bilirubin, some conditions that are associated with pathologic jaundice such as hemolysis may not be immediately jaundiced at birth. However, by 12–48 h after birth, the production of the same bilirubin that occurred in utero may result in jaundice.

Jaundice associated with breastfeeding (*breast milk jaundice*) is a benign, self-limited condition. Although a single specific cause has not been identified, substances (e.g., β-glucuronidase) in mature breast milk that promote enterohepatic uptake of bilirubin have been implicated [814–816]. This entity must be distinguished from jaundice due to "not enough breastfeeding," which is characterized by poor feed-

Table 2.2 Mechanisms of newborn jaundice (from [802])

Physiologic jaundice in the newborn
Catabolism of heme
From breakdown of fetal erythrocytes
From myoglobin, cytochromes, catalase
Decreased uptake into and excretion from liver cells
Low neonatal concentration of ligandin, the intracellular-binding protein
Low neonatal activity of uridine diphosphate glucuronosyltransferase (UD-PGT)
Nonphysiologic jaundice
Increased heme catabolism
Congenital hemolytic anemias (e.g., glucose-6-phosphate dehydrogenase deficiency, spherocytosis)
Immunologically mediated hemolysis (e.g., rhesus and ABO incompatibility)
Extravasation of blood (bruising, fractures, intracranial hemorrhages)
Decreased bilirubin conjugation and excretion
Genetic defects in UDGPT (e.g., Crigler–Najjar, Arias type 2, Gilbert)
Hepatic and biliary disease (e.g., neonatal hepatitis, intra- and extrahepatic biliary atresia)
Increased enterohepatic circulation of bilirubin
Decreased bowel passage (e.g., intestinal atresias, necrotizing enterocolitis, fasting, inadequate nutrition [breastfeeding jaundice])
Increased deconjugation of bilirubin in the bowel (e.g., breast milk jaundice)

ing, infrequent stools, and poor weight gain. Although a similar pattern of inadequate oral intake can develop during feeding with formula, association with breastfeeding requires careful assessment of maternal factors and techniques of feeding. To avoid dehydration and worsening of hyperbilirubinemia, adequate enteral feeding must be established or alternative hydration delivered (e.g., intravenous fluid) until the cause of inadequate oral intake is identified and eliminated [817].

Abnormalities in the enzymes of conjugation, anatomic malformations of the biliary system (e.g., biliary atresia), and obstructive processes (e.g., neonatal obstructive fibrosclerosing cholangiopathy) [818, 819] impair biliary function, often leading to jaundice in the first months of life. Prolonged (e.g., 2–3 weeks) and/or severe hyperbilirubinemia, development of progressive *direct* hyperbilirubinemia, and/or other signs of hepatic dysfunction (e.g., hepatomegaly, acholic stools, failure to thrive) demand meticulous evaluation to establish a definitive diagnosis. For example, without surgical intervention for biliary atresia (the *Kasai procedure*: resection of fibrotic extrahepatic biliary system and creation of a hepatoportoenterostomy) within several months after diagnosis dramatically increases the likelihood for infantile liver transplantation [820]. Of note, even after a timely Kasai, end-stage biliary cirrhosis eventually develops in 70–80% of patients, so that biliary atresia remains the most common cause of chronic end-stage liver in liver disease in children [818, 821]. Recently, the Japanese liver transplant society reported excellent long-term survival of the graft at 1, 5, 10, 15 and 20 years after a living-related liver transplant after Kasai (90.5%, 90.4%, 84.6%, 82.0%, and 79.9%). In Japan, living-related liver transplant was possible even in patients weighing less than 5 kg with early liver failure after a Kasai operation using a "reduced left lateral segments." To facilitate the success of this early intervention, effort was focused on increasing the donor pool, which decreased the mortality associated with a prolonged waiting list [822]. Although primary liver transplant for this disorder is rare, a recent report noted that "the Kasai operation has the greatest failure rate in its stated objective than any other operation in pediatric surgery. Failure to achieve any improvement in jaundice occurs in over 30% of all cases, even in the best of hands, and transplantation or listing for transplantation occurs in over half the children with type II and III BA by one year of age in countries where liver transplantation is readily available." The author suggests that primary liver transplant may offer advantages, proposing a "multi-institutional effort that is aimed at sparing more than a third of children who derive no benefit from the Kasai procedure from a futile procedure" [823]. Thus, jaundice at the one-month pediatric evaluation should prompt consideration of hepatic disease, including biliary atresia and other cholangiopathies, and possibly referral to a pediatric gastroenterologist and/or liver transplant center.

Liver dysfunction (e.g., conjugated [direct] hyperbilirubinemia) or injury frequently accompanies hemodynamic insults associated with hypoxia, ischemia, sepsis, or primary liver infection. In such cases, increased serum concentrations of liver enzymes reflect hepatocyte injury. Of importance, hepatocyte injury impairs synthetic function, manifested by reduced serum albumin concentration and/or abnormal coagulation function (i.e., prolonged prothrombin time, decreased fibrinogen levels) [824–827]. Fulminant liver failure may result from gram-negative (e.g., *Escherichia coli*) or meningococcal bacteremia or viral infections (e.g., herpes simplex, adenovirus, or echovirus) [828, 829]. With prompt restoration of perfusion or effective treatment of infection, transaminase levels (so-called liver function tests) usually decrease, but hyperbilirubinemia may persist for weeks [734].

Neonatal cholestasis commonly is associated with liver injury during parenteral nutrition, and, in this setting, increased conjugated bilirubin is associated with significant morbidity [830, 831]. Preterm infants are more vulnerable to liver injuries for a multitude of reasons, including a greater incidence of episodes of ischemia and hypoxia, of gastrointestinal and systemic infections due to immaturity of the gut epithelium, and of requiring parenteral nutrition [734, 832]. Exaggerated immune responses to inflammatory triggers such as lipopolysaccharide associated with decreased

T-cell-mediated immune modulation may also predispose the neonate to hepatic injury during systemic infection [833].

In addition to its roles as a marker of liver disease, hyperbilirubinemia can directly injure neural tissue, resulting in a neuropathologic syndrome known as *kernicterus*, the pathologic term that describes the autopsy finding of yellow-stained deep brain nuclei but sparing the neocortex. That is, although hyperbilirubinemia is usually a benign, transitional process in newborns, bilirubin-induced neurologic damage (BIND) persists as a devastating complication of severe hyperbilirubinemia [804, 834, 835]. Because experts apply the term "BIND" inconsistently, the literature categorizing the neurologic complications of hyperbilirubinemia is inconsistent and confusing. For example, in some cases, BIND includes the entire spectrum of acute and chronic injury, both mild and severe [804, 836]. Acute bilirubin encephalopathy (ABE) specifically refers to neurologic abnormalities during the first few postnatal weeks. If untreated, ABE progresses to a chronic permanent disorder, kernicterus. In other cases, experts reserve the term "BIND" for a subtle, less severe type of injury without the findings of classical kernicterus. In this schema, BIND includes abnormalities of sensory integration, central auditory processing, coordination, and muscle tone [837, 838]. Recently, Le Pichon confronted this dilemma with a detailed proposal to adopt consistent classification of the subsets of injury and establish standard diagnostic criteria for "kernicterus spectrum disorders," including defining and scoring severity, tailoring treatment, and describing short- and long-term outcome [839].

In the early stage (1–3 days), ABE includes an acute encephalopathy with nonspecific signs (lethargy, poor feeding, abnormal tone, a high-pitched cry). As the disorder progresses to an intermediate phase (4–6 days), symptoms include opisthotonos/retrocollis, seizures, and even coma. Hypotonia, active deep-tendon reflexes, and delayed motor skills predominate during the first year. Later phases include profound movement disorders including dystonia and athetosis, choreoathetoid cerebral palsy with tremor, ballismus, gaze (usually upward) abnormalities, sensorineural hearing loss, or auditory neuropathy, and, in some cases, cognitive delays [840]. This chronic phase of bilirubin neurotoxicity correlates with the pathology in the central nervous system secondary to the deposition of bilirubin in the globus pallidus, subthalamic nucleus, midbrain/pontine/ brain stem nuclei (especially related to visuomotor function), hippocampal neurons, diencephalon, central and peripheral auditory pathways, and cerebellar cells. In other infants, a more restricted injury including less severe neural hearing deficits (auditory dyssynchrony or neuropathy) and minor fine or gross motor deficits is associated with localized injury to neural pathways. Changes in EEG and auditory brain stem responses, and abnormalities on MRI (e.g., globus pallidus and subthalamic nuclei), and even death [841, 842] follow this injury. The MRI of an infant with kernicterus mirrors the distinct regional nature of bilirubin-induced neuropathology, including abnormal bilateral, symmetric, high-intensity signals in the globus pallidus and subthalamic nuclei and on occasion the internal capsule and thalamus. These structural findings are equally apparent in both preterm and term neonates with neurologic consequences secondary to hyperbilirubinemia [843].

Chronic bilirubin encephalopathy (classic kernicterus) is characterized by a tetrad of clinical signs of varying severity: movement disorders (athetosis, dystonia, spasticity, and hypotonia), auditory neuropathy, oculomotor impairments, and dental enamel hypoplasia of the permanent teeth [841]. Although the precise cellular and molecular schema of injury has not been completely defined, the injury involves inflammatory insults and neuro-excitotoxicity [804, 843]. On the other hand, the role of inflammation in this injury is complex. For example, recently, a pathway has been described that implies that bilirubin-induced proinflammatory responses can paradoxically be neuroprotective, in part secondary to antioxidant effects [844, 845].

The blood–brain barrier limits the entry of water-soluble, conjugated bilirubin as well as bilirubin that is bound to albumin [846, 847]. Therefore, in addition to increased concentrations of bilirubin (i.e., unconjugated, lipophilic form), hypoalbuminemia increases the risk of kernicterus. Furthermore, insults that impair the function of the blood–brain barrier (e.g., hypoxia, respiratory acidosis, hypothermia, sepsis, trauma, and prematurity) predispose to primary central nervous system injury from hyperbilirubinemia because of increased access of this molecule to the brain [848–851]. Thus, overall, when the level of bilirubin overwhelms neuroprotective mechanisms, brain damage ensues. But, in addition to the actual level of *unbound* bilirubin, the risk of brain injury reflects a wide range of events and complex interactions, including the duration of exposure, permeability of the blood–brain barrier, the intrinsic vulnerability of the brain (e.g., gestational and postnatal age, acidosis, inflammation, sepsis), and the response to aggressive treatment. Neurons undergoing differentiation at the time of exposure to bilirubin may be most susceptible to bilirubin's apoptosis-inducing effects [804]. The greater risk for neurotoxicity in preterm infants is exacerbated by a high incidence of concurrent disease (e.g., sepsis, respiratory acidosis), nutritional deficits (e.g., hypoalbuminemia), and frequent drug therapy (i.e., hepatic dysfunction, competition for binding to albumin and other serum proteins) [836].

By increasing the risk of hemolysis, various genetic enzyme deficiencies (e.g., glucose-6-phosphate dehydrogenase deficiency, a hereditary condition prevalent in African-Americans) [852] are also associated with neonatal hyperbilirubinemia. Reduced UDP-glucuronosyltransferase

(UD-PGT) activity can also increase the concentration of unconjugated bilirubin, especially in the setting of prematurity, sepsis, or certain defects in hemoglobin and biliary metabolism. With an incidence of ~1%, Gilbert disease is characterized by slightly decreased activity of UD-PGT, but with activity markedly impaired during physiologic stress such as infection or neonatal asphyxia [853]. In contrast, Crigler–Najjar syndrome has decreased (type II) or absent (type I) UD-PGT activity secondary to a variety of mutations [854, 855], which, if untreated, leads to unconjugated hyperbilirubinemia and irreversible neurologic injury [856]. Other genetic and environmental factors (such as UDP-GT1A1 polymorphisms) may either increase the risk of kernicterus in the presence of relatively low bilirubin concentrations or, in some cases, protect from kernicterus despite hyperbilirubinemia [857–861].

The guidelines from the American Academy of Pediatrics for the management of hyperbilirubinemia in the term and near-term neonate stress prevention of kernicterus through primary prevention (i.e., establishing appropriate nutrition to decrease enterohepatic recirculation of bilirubin), secondary prevention (i.e., early detection of high-risk infants including screening of bilirubin levels) (Fig. 2.16), and following specific protocols to initiate therapies such as phototherapy and exchange transfusion [862–864]. Compared with term infants, preterm and late preterm infants are at greater risk of kernicterus, even at lower concentrations of bilirubin [845, 865, 866]. For example, "low-bilirubin kernicterus" is a refractory cause of bilirubin neurotoxicity in the preterm infant. Hypoalbuminemia is common in preterm infants and is a consistent finding in low-bilirubin kernicterus. At the same time, preterm infants fail to demonstrate classic neuromotor signs of bilirubin toxicity. The only clinical manifestation may be recurrent apnea [843]. Treatment protocols (i.e., when to initiate phototherapy, how long to continue, indications for exchange transfusion) should be based on several variables including the trend in the absolute concentration, the rapidity of the increase in bilirubin concentration (e.g., the trend in the concentration from hour to hour), and the predicted risk (e.g., gestational and postnatal age, ongoing hemolysis, current medical status [acidosis, sepsis]) to allow more accurate and effective treatment [862]. In particular, depending on gestational age, preterm infants require scrutiny and individualized analysis due to the higher risk of neurologic injury at lower bilirubin levels in the setting of unstable and variable status and therapies. Because of limited evidence-based data, recommendations for the management of hyperbilirubinemia in preterm infants evolved from a consensus-based process with patient-specific considerations [836, 845, 867]. These references are relevant for perioperative care.

Phototherapy was first demonstrated to attenuate the serum concentration of bilirubin in 1958 [869] and then became an accepted treatment in the United States in the late 1960s [870]. Phototherapy effectively decreases the serum concentration of bilirubin by converting lipophilic bilirubin to more soluble, structural isomers (lumirubin), or configurational isomers, facilitating the excretion in a non-conjugation-dependent process [849, 871–874]. By rapidly converting bilirubin to the more polar photo isomers, phototherapy may decrease bilirubin-associated central nervous system injury. That is, phototherapy may be effective by producing photo isomers that inflict less direct neural toxicity, decreasing the transit of the more polar bilirubin photoproducts across the blood–brain barrier, or by changing the proportion of free bilirubin to total bilirubin [875, 876]. Instead of exposure to sunlight, artificial light of modern phototherapy is designed to expose the infant to light with a wavelength of 450 nm

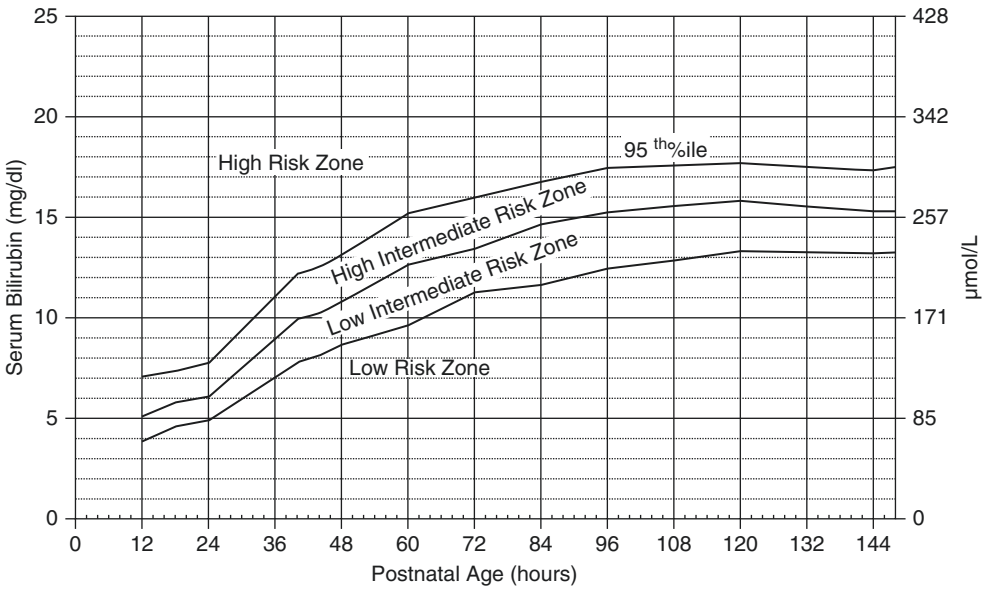

Fig. 2.16 Nomogram used to designate risk in 2840 well neonates at 36 or more weeks' gestational age with birth weight of 2000 g or more or 35 or more weeks' gestational age and birth weight of 2500 g or more based on the hour-specific serum bilirubin values. Note that this nomogram is for predicting likelihood of a subsequent bilirubin level exceeding the 95th percentile—*not* to represent the natural history of neonatal hyperbilirubinemia (from [862]; citing Bhutani et al. [868])

(blue) to avoid overheating [877]. Overall, the goal is to reduce the risk of kernicterus by decreasing the total concentration of bilirubin to less than that historically associated with kernicterus (~20 mg/dL [340 micromol/L] for healthy term babies). Phototherapy may also be used to bridge to liver transplantation in Crigler–Najjar type I [878]. Finally, phenobarbital can be used to induce UD-PGT activity in the setting of insufficiency (e.g., in Crigler–Najjar type II).

With the improvements in phototherapy, the need for exchange transfusion for neonatal jaundice (first found to be effective in 1951) [879] has all but disappeared [849, 880]. If an exchange transfusion is required, one or two central venous catheters are placed, and small aliquots of blood are removed and then replaced with a mixture of donor (and bilirubin-free) RBCs and plasma (or albumin). Infusion of albumin before the exchange transfusion may increase the amount of bilirubin removed during the procedure [881]. In addition to decreasing the bilirubin concentrations, exchange transfusion may reduce circulating antibody concentrations during ongoing hemolysis. Severe complications in approximately 2% of patients undergoing exchange transfusion [882] include problems associated with central line placement (thrombosis, bleeding) and necrotizing enterocolitis [883], electrolyte disturbances, and thrombocytopenia. Currently, exchange transfusions are recommended only to treat acute bilirubin encephalopathy or hyperbilirubinemia resistant to phototherapy. Levels of total serum bilirubin at which exchange is recommended vary with associated risk factors (e.g., isoimmune hemolytic disease, G6PD deficiency, signs of sepsis or asphyxia, gestational and postnatal age, and the bilirubin–albumin ratio) [862].

Clinical Significance and Summary

Immature and/or abnormal hepatic function in the neonate presents several challenges in the setting of anesthesia and surgery. Some medications (e.g., ceftriaxone, furosemide, and oxacillin, but not methicillin) compete with bilirubin for albumin-binding sites. If displaced from albumin, the proportion of unbound or "free" bilirubin concentration increases, exaggerating the risk for neurotoxicity from this molecule crossing the blood–brain barrier [884, 885]. Of note, in some cases, a preservative or other additive to a pharmacologic preparation rather than the drug itself may displace bilirubin from albumin (e.g., the sodium benzoate in intravenous diazepam) [886].

Acidemia exaggerates bilirubin neurotoxicity primarily by its effects on bilirubin solubility and the decreased binding of protonated bilirubin to albumin [848, 849, 887]. Neurologic injury associated with a given level of bilirubin may vary as a function of the effectiveness of protective mechanisms that determine the relative transport into and out of the brain. That is, the active transport of bilirubin from the brain into the blood may diminish injury, but acidemia may inhibit this activity [887]. Similarly, the severity of the injury depends on both the duration and concentration of unbound bilirubin in the vulnerable developing brain, since the immature brain may be particularly at risk for apoptosis and necrosis, especially in the presence of infection or other stressors [841].

The neonatal anesthesiologist must appreciate that the critically ill neonate who is at high risk for hemodynamic and respiratory instability and associated respiratory or metabolic acidosis, hypoalbuminemia, and liver dysfunction may at the same time incur increased risk for bilirubin neurotoxicity. Hepatic dysfunction and immaturity may disrupt the normal metabolism of drugs including commonly used anesthetic agents (e.g., muscle relaxants). Finally, hemostasis must be meticulously evaluated preoperatively and aggressively monitored and treated intraoperatively.

Renal Function (also See Chap. 8

In utero, the placenta maintains fetal metabolic and electrolyte homeostasis. Permanent kidneys appear during the fifth week of gestation and nephrons during the eighth week, initially in the juxtamedullary region and cortex. A complex interaction of genes (e.g., Wilms' tumor gene 1 [WT1] and growth factors [neurotrophic factor {GDNF}]) orchestrates this process [888, 889]. By 20 weeks' gestation, one-third of the full complement of nephrons has developed [890]. By 35–36 weeks' gestation, the number of nephrons equals that of the normal young adult [891]. When the full complement of nephrons is reached, the kidneys mature by increasing both glomerular and tubular size; no new nephrons/glomeruli develop. Infants born prematurely develop new nephrons until about 34–35 weeks postconceptional age. More than 60% of nephrons form during the third trimester [892]. Vascular growth and development parallel nephrogenesis.

The degree of renal immaturity in preterm infants is inversely proportional to the gestational age. Nephrogenesis stops at 40 days after birth [893]. In some cases, this event results in a low endowment of nephrons and consequent hypertension and endothelial dysfunction [21, 26, 894], an example of the phenomenon of "Developmental Origins of Adult Disease" (see Introduction). In addition to interrupting normal organogenesis of the kidney and its vascular bed, prematurity and intrauterine growth restriction both inflict negative effects on postnatal renal growth [30, 31, 895].

The number of nephrons varies by up to fivefold among mature, healthy term infants. The number of nephrons per kidney averages approximately 1 million but ranges from about 300,000 to over 2 million [896]. Infants born at term

with a smaller-normal endowment of nephrons are at greater risk for systemic hypertension and other cardiovascular and renal diseases as are preterm infants [19, 897]. Both genetic and environmental factors may account for the reduced number of nephrons [30, 31, 898]. Chromosomal anomalies, copy number variants, and monogenic abnormalities combine to account for 30–50% of congenital abnormalities of the kidney and urinary tract [899]. Mutations in HNF1B, the gene encoding hepatocyte nuclear factor 1β, are the most commonly identified genetic cause of renal malformations [900, 901]. Of note, HNF1B-associated disorders extend beyond the kidney (e.g., genital tract anomalies, pancreatic hypoplasia, abnormal liver function) [902]. A polymorphism of the RET gene is associated with a decreased number of nephrons [903, 904] and a common variant Pax2 with smaller kidneys at birth [905]. Interaction between HNF1B and Pax2 may be crucial to the normal development of the kidney and urinary tract, with mutations associated with multi-cystic and/or hypoplastic kidneys [906]. Finally, environmental factors (intrauterine growth restriction, hyperglycemia, exposure to cocaine or alcohol) contribute to abnormal renal and urinary tract development [899]. Specific maternal medications such as angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, glucocorticoids, and anti-seizure medication (and others) have been associated with renal agenesis and anomalies [899]. Finally, oxidative injury during the neonatal period has been associated with decreased capillary density and fewer nephrons in adult rats [907].

Urine is first formed by 10 weeks' gestation, and production increases from about 2–5 mL/h at 20 weeks' gestation to 10–12 mL/h at 30 weeks, 12–16 mL/h at 35 weeks, and 35–50 mL/h at 40 weeks' gestation [908]. The fetal kidneys produce large volumes of hypotonic urine essential to maintain normal amniotic fluid volumes, especially after 18 weeks' gestation. In turn, large volumes of fetal urine are necessary for normal pulmonary development. For example, oliguria resulting in oligohydramnios is associated with specific facies, clubfeet, limb contractures, and, in severe cases, pulmonary hypoplasia (Potter's sequence/oligohydramnios sequence).

Developmental Changes in Distribution of Total Body Water

At 16 weeks' gestation, the total body water accounts for 94% of the fetus' weight; at 32 weeks' gestation, 82%; and at term, approximately 75%. The size of the extracellular compartment decreases from 65% at 16 weeks to about 60% at 24–25 weeks' gestation and then to about 45–50% at term, decreasing to approximately 30% at 6 months and then 20% by adolescence. At the same time the intracellular compartment increases from 34% in early gestation to 40–50% at term [909, 910] and peaks at approximately 3 months of age [911]. During the first 3–7 days of extrauterine life, healthy term infants lose about 5–10% of their body weight, primarily through contraction of the extracellular water space; preterm infants <1500 g may lose 10–15% of body weight [911]. Transepidermal fluid loss is related to gestational age and can be as much as 60–100 mL/kg/day in ELBW infants. Over the first 5 days of life, fluid losses decrease dramatically (from 45 to about 19 g/m^2/h) in infants at 25–27 weeks' gestation [912]. During the first few postnatal days, naked preterm infants lose up to 15 times more water through evaporation than naked term infants [913]. Naked VLBW infants may lose up to 10% of their body weight through evaporation during the first 24 h of life. Although decreasing over the first postnatal weeks, the transepidermal water loss of an ex-24-week gestation infant is twice that of a term infant at 28 days [914].

At least in part, the "contraction" of the extracellular compartment has been linked to atrial natriuretic peptide, a hormone produced in and released from the myocardium in response to stretch of the atrium. Increased left atrial pressure associated with increased pulmonary blood flow at birth triggers the release of atrial natriuretic peptide [915].

GFR and Blood Flow

Fetal and neonatal renal function is characterized by reduced renal blood flow, glomerular filtration rate (GFR), solid excretion, and concentrating capacity. In part, renal blood flow is reduced in utero because of increased renal vascular resistance. After birth, renal blood flow improves markedly due to increased arterial blood pressure and decreased renal vascular resistance, which allow more of the cardiac output to flow to the kidneys (2–4% in utero, 10% at 1 week of age, 25% in the adult). Renal blood flow is about 20 mL/min/1.73 m^2 at 30 weeks, 45 mL/min/1.73 m^2 at 35 weeks, 80 mL/kg/1.7 m^2 at term, 250 mL/min/1.73 m^2 at 8 days, and 770 mL/min/1.73 m^2 at 5 months of age [916]. Similarly, GFR increases rapidly in utero as the number of nephrons increases. Because growth of the fetal kidney begins deep in the medulla, the juxtamedullary nephrons are more mature than other nephrons at birth and have greater tubular length than outer and inner cortical nephrons. Since the glomeruli are distributed uniformly, a "tubular–glomerular" imbalance exists, which allows less efficient reabsorption of substrates presented to the proximal tubules of the neonate.

The GFR in preterm infants is a function of both gestational and postnatal age. During the first 24 h of extrauterine life, the GFR of infants born before 25 weeks' gestation may be as low as 2 mL/min/1.73 m^2. Infants born between 25 and 28 weeks' gestation have a GFR of 10–13 mL/min/1.73 m^2 and those born after 34 weeks' gestation, 20–25

mL/min/1.73 m^2, which is similar to that of full-term infants [917]. Although GFR increases at a slower rate in ELBW infants, all neonates without acquired renal insufficiency double GFR by two weeks of age and triple the value by three months of age. Thereafter, GFR increases more slowly. A multicenter study from France reported GFR measured in infants of 27–31 weeks' gestation over the first month of life [918]. Although the precise values in GFR (mL/min/1.73 m^2) varied from previous studies, the general trend for increase is similar and reflects an approximate doubling over the first month, between day 7 and day 28 of life (day 7, 18.5 ± 12.6; day 14, 20.6 ± 13.1; day 21, 22.2 ± 11.7; day 28, 26.2 ± 19.6). The increase correlates inversely with gestational age.

Adult values for GFR are reached by 12–24 months of age. Due to rapid renal maturation after birth, a 3-week-old, ex-27-week gestation infant may have significantly more mature renal function than a normal 6-h-old term infant. The kidney matures in response to "demand" (separation from the placenta plus solute exposure). That is, renal filtration and concentrating ability increase when the kidneys are exposed to a substrate [919].

At birth, serum creatinine reflects maternal values since this molecule is freely exchanged via the placenta. Furthermore, the placenta, not the fetal kidney, regulates metabolic stability in utero. Serum creatinine in the neonate is greater than that of normal 1–2-week-old term infant (0.4 mg/dL), reflecting both placental transfer to the fetus from the mother and reabsorption via immature renal tubules [894, 920] especially in the preterm infant. For at least 3 days after birth, the serum creatinine in the neonate correlates with maternal values [921]. For the first 4 weeks of life, the serum creatinine in preterm infants exceeds that in term infants [922]. Interestingly, the serum creatinine at birth in infants born before 27 weeks was the same as those born at 31–32 weeks' gestation, increased in all groups over the first 3 days of life, and then gradually decreased to <0.5 mg/dL [923]. However, the maximum serum creatinine concentration reported was greater and occurred later (day 3.5 vs. day 1) in the most immature neonates. Creatinine clearance increased in all groups but increased more slowly in the <27-week gestation infants.

The variability in GFR and creatinine clearance, as a function of gestational and postnatal age, implies that estimating GFR by tracking the serum concentration of creatinine may be unreliable; the degree and duration of an increase in the serum creatinine depend on the degree of prematurity. That is, creatinine is reabsorbed in the immature tubules for at least three weeks after birth, but at the same time, the lower mass of nephrons, fluid loss/shifts, and the neonatal cardiovascular transition (e.g., cardiac output, blood pressure, renal blood flow), especially the ELBW, add to the variability of this marker in the first weeks of life. The *normal range* of the serum concentration of creatinine is wide and varies with both gestational and postnatal age. The components of microvascular filtration at the level of the glomerulus vary with maturation. That is, the rate of filtration increases as the number of nephrons increases up to 36 weeks' gestation, so that the preterm infant has an additional variable that contributes to the effective GFR. Therefore, while establishing clinical criteria for other biomarkers, investigators have generated a variety of innovative formulae to estimate GFR (based on creatinine) in the neonate and young infant [924].

Of clinical importance, estimating the clearance of drugs that depend on the kidneys for elimination may be challenging in the neonate. Because renal function is immature, the serum concentrations and half-lives of drugs often differ from values in adults, particularly during the first weeks to months of postnatal life of the preterm infant. Given the unique aspects of neonatal physiology, various formulae that calculate the "estimated" GFR may underestimate the GFR in this age group. Thus, methods to evaluate renal function in the neonate are evolving beyond estimating "creatinine clearance."

Although creatinine is freely filtered in the glomerulus, not metabolized, and not protein-bound, the secretion of this molecule in various disease states (e.g., AKI) at any age, or, in the case of the neonate, reabsorption in the renal tubules, estimating GFR based on serum creatinine and various formulae may over- (secretion) or underestimate (reabsorption) the "true" GFR. Creatinine is a standard but not ideal marker of GFR, especially in the neonate. Furthermore, because the level is stable until 25–50% of renal function is lost, serum creatinine does not predict nor reflect early acute kidney injury (AKI) [924]. Finally, hepatic function, muscle mass/catabolism, and fluid status influence creatinine clearance, particularly in the neonate. Recently, experts [20, 921, 924–926] propose that markers, such as cystatin C (CysC), beta-trace protein (BTP), urine neutrophil gelatinase-associated lipocalin (NGAL), and others may more reliably define GFR and detect kidney injury as well as predict clearance of some drugs. A panel of biomarkers may eventually provide the most accurate system for diagnosing and evaluating AKI in the neonate and beyond.

CysC is a low-molecular-weight endogenous protein that is filtered by the glomeruli, and levels are independent of muscle mass, age, and sex. Recently, in both term and preterm infants, a formula incorporating serum CysC has been developed to accurately estimate GFR [927]. To improve reliability, some methods and novel formulae incorporate body surface area and total kidney volume (determined by ultrasound) [924]. However, the analytical methods to measure this biomarker to assess renal function are evolving and currently remain expensive. Some suggest that combining data for creatinine and CysC may fine-tune diagnostic criteria for renal function and improve criteria for AKI in infants. Currently, although BTP may offer advantages as a marker to estimate GFR, tools for clinical analysis remain experimental.

Because serum creatinine estimates GFR, not renal injury, the level fails to increase for days after an insult, so that the effort to mainstream novel biomarkers is urgent in the setting of predicting, diagnosing, and treating acute kidney injury (AKI). In the neonate, this will demand defining developmentally dependent (gestational age, postnatal age) standards as well as developing the specific analytical framework for easy measurement. One report suggests that CysC levels are independent of gestational age, birth weight, and gender [928], but these data must be validated. For now, guidelines for defining and evaluating AKI in clinical practice are tied to serum creatinine and urine output, with recent efforts to standardize definitions and stratify risk and severity (pediatric RIFLE [risk, injury, failure, loss, and end-stage renal disease], and AKIN [Acute Kidney Injury Network]) specifically in the neonate [929].

Renal Tubular Function

Extracellular fluid volume, water balance, and sodium and other electrolyte concentrations are interrelated and undergo significant change postnatally. In addition to the dramatic development in the number of nephrons, glomerular function, and renal blood flow, the renal tubules mature throughout fetal and postnatal life. Of note, tubular immaturity accounts for inefficient salvage of essential substrates (e.g., glucose, amino acids). The metabolic demands of rapid growth and/or illnesses coupled with immature renal function complicate managing fluids and providing nutritional support to the newborn.

Similar to other epithelia, renal tubular cells are polarized. That is, specific, unique channels, transporters, and other proteins populate the apical (facing the urine) versus the basolateral membrane (facing the blood), which provides the mechanism for net movement of solutes both from the lumen to the capillary (reabsorption) and vice versa (secretion). This distribution of proteins to each membrane defines the anatomically and functionally distinct sections of the renal tubules and allows the kidney to salvage most substrates from the glomerular filtrate in the proximal tubule and fine-tune water and solute content in the more distal segments. For example, although sodium is absorbed along the entire system, the proximal tubules reabsorb 60–80% of filtered sodium and water. As well, glucose, phosphate, and most amino acids are salvaged primarily along the proximal tubule. The loops of Henle, the distal tubules, and the collecting tubules concentrate urine and secrete potassium. An additional 10–15% of filtered sodium is absorbed in the distal (aldosterone responsive) and collecting tubules (antidiuretic hormone determines water permeability). The amount of sodium in fluid presented to the distal tubules depends, in part, on the efficiency of the transport mechanisms of the proximal tubule.

The membrane proteins (transporters) that salvage amino acids, glucose, bicarbonate, and phosphate from the glomerular filtrate are located on the apical membrane of the proximal tubule and are "active" transporters (i.e., requiring energy to move substrates across the membrane against their concentration gradient). The simultaneous movement of sodium down its electrochemical gradient generates the energy for the transport of the substrate against its concentration gradient. For example, glucose and amino acids are cotransported with sodium across the apical membrane. Other substrates are counter-transported (e.g., H^+ and sodium) with sodium moving in the direction opposite to that of the substrate (i.e., exchange mechanism). The sodium gradient then must be reestablished, which is mediated by the activity of the Na^+–K^+-ATPase pump. This metabolic role of the Na^+–K^+-ATPase pump in maintaining the sodium gradient for all eukaryotic cells is critical. Located on the basolateral membrane, the activity of this enzyme accounts for approximately 70% of renal oxygen consumption.

Development of Sodium-Driven Transport Function

Tubular reabsorption of water and solutes must match the fourfold increase in GFR over the first 2 years of life. That is, "if there was no increase in solute and water reabsorption that parallels the increase in glomerular filtration, the neonate would become volume-depleted with a minor developmental increase in glomerular filtration rate" [930]. That is, when the filtered load of sodium increases with greater GFR, resorption must similarly increase to avoid dehydration and the loss of electrolytes. This correlation between GFR and transport, glomerulotubular balance, persists throughout life so that tubular transport parallels changes in GFR (e.g., in response to extracellular fluid volume). The proximal tubule reabsorbs most of the solutes from the isotonic glomerular filtrate (all amino acids and glucose, 80% of bicarbonate, and approximately 70% of the "chloride") [930], mostly via sodium-dependent transport. These active transport processes are linked to the extracellular-to-intracellular gradient maintained by Na^+–K^+-ATPase.

After birth, thyroid hormone and corticosteroids seem to induce the developmental increase in function of sodium-driven transport, both by quantitative effects and by changes in isoform expression [930]. For example, the activity of the apical sodium–hydrogen exchanger (NHE) increases dramatically in the first 24 h after birth and then more slowly during postnatal life. This protein acidifies the urine while functioning to mediate the bulk of transepithelial sodium reabsorption. [915]. At the same time, reabsorption of sodium in the proximal tubules increases 5–10-fold as Na^+–K^+-ATPase activity [931] increases, in part secondary to developmental changes

in its regulatory β-subunit. That is, the fetal β2 isoform (which is present in both the apical and the basolateral membranes) is downregulated after birth, and β1 is upregulated and targeted only to the basolateral membrane [932]. The functional, mature enzyme consists of a heterodimer of α1 and β1 subunits. Glucocorticoid hormones increase mRNA for both subunits of this enzyme, and prenatal administration of betamethasone to the mother in preterm labor to induce maturation of the lungs may also mature renal function. Finally, maturational increases in sodium reabsorption have been identified in the thick ascending loop (reabsorbs 25% of filtered sodium), linked to developmental changes in both the apical Na+-K+-2Cl- (NCKK2) and basolateral NCKK1cotransporters [915].

The proximal tubule increases its capacity for absorption with advancing gestational age. Five percent of the filtered sodium is excreted in the urine of <30-week gestation infants, but only 0.2% is excreted in term infants [933]. However, fractional excretion (FE_{Na}) decreases over the first month. For example, in <28-week gestation infants, although FE_{Na} was >6% on day three of life, the value was 4% at the end of the first week and 2% by 1 month [934]. Hypoxia, respiratory distress, and hyperbilirubinemia may increase fractional sodium excretion. In general, the urinary sodium loss in the preterm infant (e.g., 2-week-old, 23-week gestation infant) may be as high as 8 mEq/kg/day, a value that exceeds the commonly recommended nutritional requirement of 2–4 mEq/kg/day [915]. Since sodium is critical for growth and development, vigorous repletion is critical in ELBW infants.

Neonates concentrate urine to a more limited degree than adults (245–450 mOsm/L in preterm infants vs. 600–800 mOsm/L in term infants vs. 1200–1400 mOsm/L in adults). Similarly, neonates >35 weeks' gestation can dilute their urine to adult levels (~50 mOsm/L) and infants <35 weeks' gestation to about 70 mOsm/L [935], but neither can excrete a water load as rapidly as the older child. That is, the maximum urinary osmolality attained after a dose of DDAVP was only ~520 mOsm/kg in 30–35-week gestation infants and 570 mOsm/kg in 4–6-week-old infants born at term. A 6-month-old child concentrates urine to 1300–1400 mOsm/kg after a dose of DDAVP [917]. The majority of infants 6–12 months of life remain unable to maximally concentrate their urine.

The limit in concentrating capacity of the immature kidney is not related to the absence of arginine vasopressin (antidiuretic hormone [ADH]). In fact, at birth ADH levels are increased in both preterm and term infants, but decrease rapidly postnatally (see Renin–Angiotensin System) [936]. The immature corticomedullary osmotic gradient and low GFR may contribute to the limited ability to both maximally dilute and concentrate urine.

The concentration of serum electrolytes in the neonate, especially the preterm, reflects renal tubular immaturity. For example, the reduced serum concentration of bicarbonate in the neonate (12–16 mEq/L in ELBW infants and 18–20 mEq/L in 30- to 35-week gestation infants compared with 20–22 mEq/L in term infants and 25–28 mEq/L in adults) [937] develops secondary to the urinary loss of bicarbonate, primarily in the proximal tubule, which leads to urine with an alkaline pH and a mild serum metabolic acidosis. The Na^+/H^+ antiporter (NHE) plays a major role in secreting protons in exchange for bicarbonate and undergoes dramatic developmental changes. Although at least six different isoforms have been identified, NHE-3 (present in the proximal tubule and the thick ascending loop) is responsible for ~90% of bicarbonate reabsorption as renal function matures postnatally, compared with ~60% in the perinatal period [938]. Both glucocorticoids [939] and thyroid hormone [940] facilitate the maturation of this transporter. Age-related differences in NHE may contribute to differences in the acid–base balance among newborns and older children/adults. Hydrogen is actively secreted, and the secreted ion reacts with bicarbonate to produce carbonic acid and carbon dioxide. These substances enter the tubular cells through the action of carbonic anhydrase. In addition to age-related dysfunction of NHE, carbonic anhydrase function may also be immature.

Glucose is reabsorbed in the proximal tubule via the sodium–glucose cotransporter (SGLT-2), and, similar to other carrier-mediated transporters, developmental changes have been documented [941]. In preterm infants, tubular reabsorption is decreased so that glucosuria is common. The tubular reabsorption of glucose and the transport maximum (T_m) (150 mg/dL in term neonates compared with 180 mg/dL in older children and adults) are both decreased in the neonate. Preterm infants less than 34 weeks' gestation have a greater fractional excretion of glucose and a reduced maximal reabsorption compared to full-term infants [942]. Finally, calcium absorption occurs in the proximal tubules of the kidneys, primarily by passive diffusion, but the large renal loss of sodium increases calcium excretion. Sick neonates, especially preterm neonates, require supplemental intravenous calcium to maintain normal ionized calcium concentrations.

Serum potassium concentrations that exceed 5.0 mmol/L are relatively common in the neonate, particularly in preterm infants with a mild metabolic acidosis. Non-oliguric hyperkalemia (serum potassium >6.5 mmol/L in the absence of renal failure) is characterized by a rapid increase in the serum potassium during the first one to three days after birth and develops frequently in ELBW infants. In contrast to older infants, children, and adults, this hyperkalemia is not secondary to abnormal potassium excretion or excessive intake, but instead seems to result from rapid shifts of potassium from intra- to extracellular compartments [943, 944] and is associated with abnormal Na^+–K^+-ATPase activity in eryth-

rocytes [945]. As in older children and adults, the treatment of hyperkalemia includes insulin/glucose, calcium/bicarbonate, diuretics, albuterol, peritoneal dialysis, and binding resins. In neonates, exchange transfusion should also be considered [944].

Renin–Angiotensin System

Hormonal control of neonatal fluid and electrolyte homeostasis is complex and, in some ways, unique compared with the older child and adult. The renin–angiotensin–aldosterone system exerts a particularly central role in maintaining homeostasis of sodium and other electrolytes. Renin has been identified as early as 17 weeks' gestation, and plasma renin activity (PRA) is inversely correlated with gestational age (60 mg/mL/h at 30 weeks; 10–20 mg/mL/h at term) [946] but remains at least threefold greater in the neonate than in the adult [947, 948]. The substantial PRA is associated with increased serum aldosterone (see below) compared with adults [949]. Also, hypoxia [950] and hypovolemia [951] increase renin and angiotensin II levels. However, although angiotensin II may moderate a variety of renal hemodynamic effects, the tubular function of the neonate seems insensitive to this molecule [915].

Inherited renal tubular dysgenesis (absence or poor development of proximal tubules and associated anuria, leading to oligohydramnios and the Potter sequence), usually a fatal disorder, has been linked to mutations in the genes encoding the components of the renin–angiotensin system (angiotensinogen, renin, angiotensin-converting enzyme, or angiotensin II receptor type 1). Similar outcomes are associated with secondary renal tubular dysgenesis [952]. Thus, although the specific role of the plasma renin activity in utero is not completely defined, the donor twin of severe twin-to-twin transfusion syndrome, congenital hemochromatosis, exposure to renin–angiotensin inhibitors, or administering angiotensin-converting enzyme (ACE) inhibitors to mothers has been associated with anuria–oligohydramnios, pulmonary hypoplasia, growth retardation, and renal tubular dysplasia in the fetus [953].

Although the fetus has access to aldosterone both from the mother and from the fetal adrenal, the fetal kidney is less responsive to this hormone than after birth. Aldosterone concentrations are directly related to gestational age, being greater in the preterm infant than in the adults. Nonetheless, the neonate is considered "aldosterone resistant" based on the greater urinary sodium loss despite large concentrations of aldosterone. Since aldosterone activates the mineralocorticoid receptor to initiate sodium reabsorption and potassium excretion, the finding of ineffective expression of this factor provides a framework for the "pseudohypoaldosteronism" in the neonate. The gradual maturation of the tubules to aldosterone probably reflects the increased expression of the mineralocorticoid receptor and associated mediators. In a recent study in neonates born at <33 weeks' gestation, 33–36 weeks, and term, aldosterone secretion was reduced in the two groups of preterm infants (serum levels correlated directly with gestational age), and sodium wasting correlated inversely with gestational age. However, in contrast to term and moderately preterm infants who exhibited insensitivity, the very preterm infants (<33 weeks' gestation) exhibited a transitory sensitivity to aldosterone; resistance developed over the first month. The clinical relevance of these data to the very preterm infants is unclear [954].

Prostaglandins play a role in maintaining GFR and renal blood flow, primarily by counterbalancing the vasoconstrictive effects of the renin–angiotensin system. The excretion of PGE_2 and prostacyclin metabolites is fivefold greater in the preterm compared with the term infant and 20-fold greater than that of the older child [955]. Of importance, the renal failure associated with indomethacin given to close a patent ductus arteriosus has been correlated with the vasoconstriction induced by the inhibition of prostoglandins.

The concentration of plasma vasopressin (antidiuretic hormone [ADH]) is greater in neonates than later in life, especially after vaginal delivery [956], and is considered responsible, in part, for the reduced urine output during the first 24 h of life. Vasopressin may lead to the contraction of the extracellular volume immediately after birth and may contribute to the indomethacin-induced renal failure in preterm infants. Hypoxia, atelectasis, intraventricular hemorrhage, and BPD increase urine ADH concentrations in both preterm and term infants [957].

Clinical Significance and Summary

Managing fluids and electrolytes in the neonate demands an in-depth knowledge of renal developmental physiology, especially related to sodium and water excretion and glucose homeostasis. Analyzing ongoing requirements for sodium, potassium, calcium, and glucose is essential preoperatively to estimate maintenance fluid delivery, as well as to predict an approach to intraoperative losses and to assess the need for monitoring laboratory values during surgery. In the setting of cardiorespiratory and central nervous system immaturity and vulnerability, normalizing intravascular volume and serum electrolytes preoperatively may enhance intraoperative stability. Although intraoperative events often demand rapid infusion of crystalloid and/or colloid, maximizing preoperative stability can only contribute to minimizing wide fluctuations in cardiovascular parameters perioperatively.

Providing a warm, humidified environment and inspired gases intraoperatively and minimizing transepidermal fluid

loss during transport (i.e., plastic shields, head covers), especially in the ELBW infant, are essential aspects of fluid and electrolyte therapy (see Chap. 8).

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Anesthesia and Ancillary Drugs and the Neonate

3

Brian J. Anderson and Jerrold Lerman

Introduction

Neonates are a heterogeneous population characterized by a limited weight or size range. They are the group of children from birth 28 days of postnatal life and include both preterm (i.e., born before 37 weeks gestational age) and term neonates. In practice, the word "neonate" extends to former preterm neonates. Consequently, postmenstrual age (PMA) may range from extreme preterm birth at 22 weeks up to 50 weeks PMA, while weight may range from 0.5 to 5 kg. Age, size, comorbidity, coadministration of drugs, and genetic polymorphisms contribute to the extensive interindividual pharmacokinetic (PK) and pharmacodynamic (PD) variabilities in this population. These phenomena distinguish neonates as a specific population with major pharmacological differences from their older counterparts. Although the general principles of clinical pharmacology also apply to neonates, their characteristics warrant a tailored approach. History provides us with evidence of the deleterious effects of failure to account for the pharmacological differences of this age group including chloramphenicol (gray baby syndrome) and benzyl alcohol (gasping syndrome) in neonates. As well, bupivacaine toxicity in those receiving long-term epidural infusions [1, 2] and acute fentanyl tolerance [3] are two examples in anesthesia practice of side effects in neonates.

Effective and safe pharmacotherapy depends upon an understanding of the clinical PK and PD properties of the drugs employed. Besides age-dependent differences in PK and PD, differences in adverse effects should also be considered. Although the available data on drug disposition and its effects in the neonate have increased considerably in the past few years, PK-PD interactions for many drugs remain poorly understood. Clinical studies in neonates present multiple challenges and difficulties, of which ethical issues, the perceived high vulnerability, technical difficulties, lack of self-assessment, immaturity, and the need for specific formulations are salient examples. However, recent progress has improved the feasibility and the clinical relevance of such studies in neonates. Models have been developed to handle extensive between-individual variability in PK and PD parameter estimates and to formulate dose estimation [4]. Also, population-based modeling tools have helped to quantify the pharmacodynamics [5].

Two major considerations that influence drug action in children that are unimportant in adults are growth and maturation. How these factors interact is not necessarily transparent from simple clinical observations, because they correlate very closely. Drug elimination may increase with weight, height, age, body surface area, and creatinine clearance. One approach is to standardize for size before incorporating a factor for maturation and organ function [6]. By adopting such an approach, one may directly compare pharmacokinetic variables in neonates with those in older children and adults to determine appropriate drug dosing [7, 8].

Disentangling Pharmacokinetic Covariates in Neonates

Size

Allometry is a term used to describe the nonlinear relationship between size and function. This nonlinear relationship is expressed as

$$y = a \cdot \text{BodyMass}^{PWR},$$

where y is the variable of interest (e.g., basal metabolic rate (BMR)), a is the allometric coefficient, and PWR is the allometric exponent. The value of PWR has been the subject of

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much debate. BMR is the most common physiological variable investigated, although camps are divided over its *PWR* value; 2/3 (i.e., body surface area) or 3/4.

In all species studied to date including humans, the relationship between the log of the BMR and the log of body weight is a straight line with a slope of 3/4 (Fig. 3.1). Fractal geometry mathematically explains this phenomenon [10, 11]. The 3/4 power law for metabolic rates was derived from a general model that describes how essential materials are transported through space-filled fractal networks of branching tubes. A great many physiological, structural, and time-related variables scale predictably within and between species with weight (*W*) exponents (*PWR*) of 3/4, 1 and 1/4, respectively [12].

These exponents have applicability to pharmacokinetic parameters such as clearance (CL, a physiological process), volume (*V*, a structural variable), and half-time ($T_{1/2}$, a time-related variable) [12]. The factor for size (*Fsize*) for total drug clearance may be expected to scale with a power of 3/4:

$$Fsize = \left(W/70\right)^{3/4}$$

The weight-based clearance of the analgesic drug tramadol is similar in several mammalian species with human allometric prediction (Fig. 3.2).

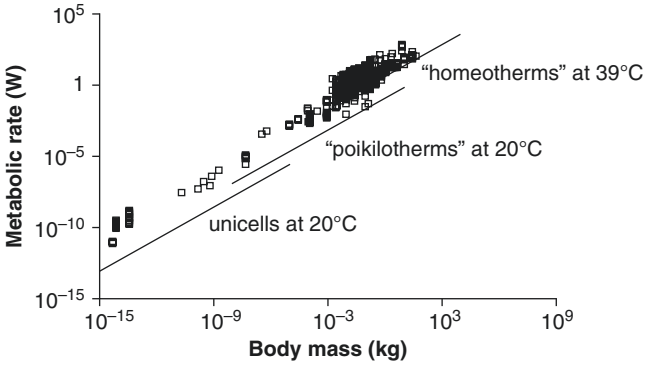


Fig. 3.1 A comparison of the temperature-standardized relation for whole-organism metabolic rate as a function of body mass. The "allometric 3/4 power model" fits for unicells, poikilotherms and homeotherms, uncorrected for temperature, are also shown. From Gillooly JF et al. Effects of size and temperature on metabolic rate. (Gillooly JF et al. Effects of size and temperature on metabolic rate. (Science 2001; 293: 2248–2251, with permission)

Maturation

Allometry alone is insufficient to predict clearance in neonates and infants from adult estimates [13–15]. (Fig. 3.3) The addition of a model that describes maturation is required [17]. The sigmoid hyperbolic or Hill model [18] is useful for describing this maturation process (MF):

$$MF = \frac{PMA^{Hill}}{TM_{50}^{Hill} + PMA^{Hill}}$$

The TM_{50} describes the maturation half-time, while the Hill coefficient relates to the slope of this maturation profile. There may be asymmetry about the point of inflection, and

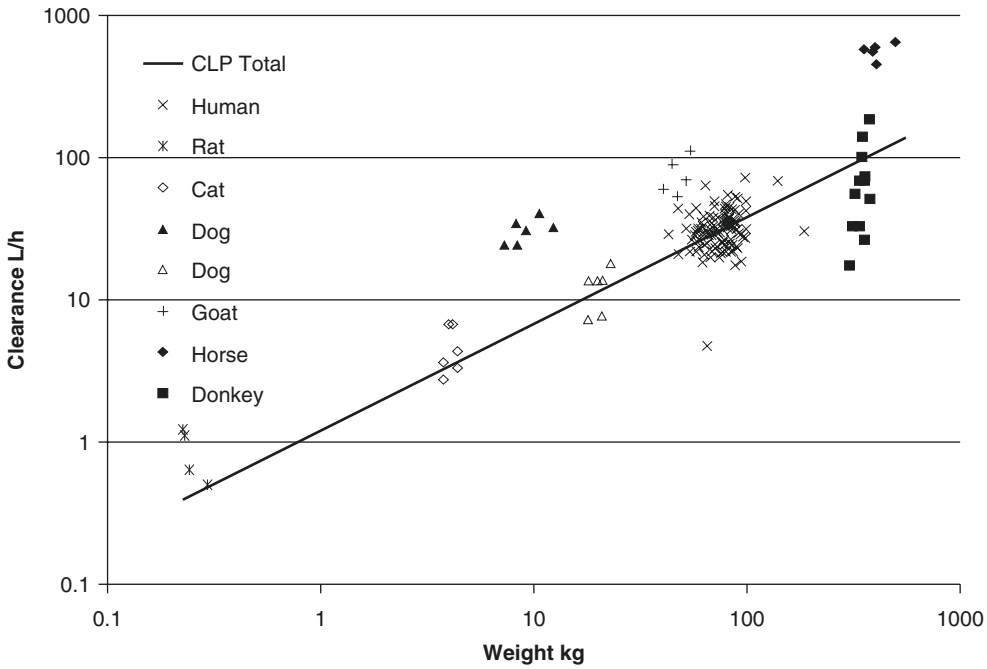


Fig. 3.2 Weight-predicted tramadol total clearance (CLP total) compared to human allometric prediction using a 3/4 power exponent (solid line). From Holford S. J Pharmacol Clin Toxicol 2014;1:1023, with permission

the addition of an extra parameter describing this asymmetry can be used to provide extra flexibility for this empirical function [19].

Maturation of clearance begins before birth, suggesting that PMA would be a better predictor of drug elimination than postnatal age (PNA). The fetus is capable of metabolizing drugs. Hepatic drug metabolism activity appears as early as 9 to 22 weeks' gestation when fetal liver enzyme activity may vary from 2% to 36% of adult activity [20–22]. These pathways then mature at different rates. Microsomal enzyme activity can be classified into three groups: (i) mature at birth but decreasing with age (e.g., CYP3A7 responsible for methadone clearance in neonates [23]; (ii) mature at birth and sustained through to adulthood (e.g., plasma esterases that clear remifentanil [24]; and (iii) immature at birth [25].

Transition from the intrauterine to the extrauterine environment is associated with major changes in blood flow. There may also be an environmental trigger for the expression of some metabolic enzyme activities that result in a slight increase in the maturation rate above that predicted by PMA at birth (Fig. 3.4) [16, 26]. Many biotransformation reactions, especially those involving certain forms of cytochrome P-450, are inducible before birth through maternal exposure to drugs, cigarette smoke, or other inducing agents. Postnatally, biotransformation reactions may be induced through drug exposure and may be slowed by hypoxia/

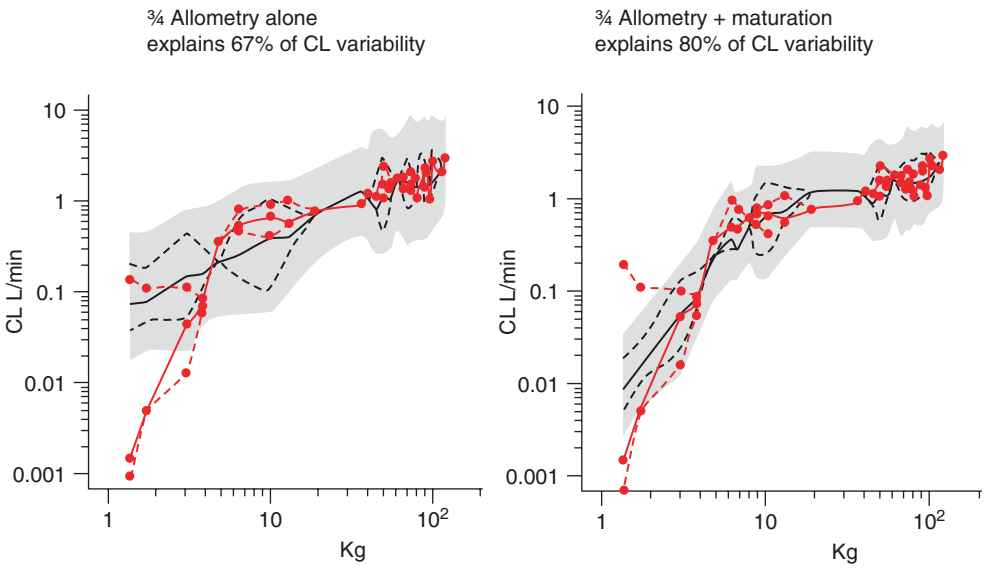


Fig. 3.3 Size and maturation explain much of propofol variability. Original data from Ref 15. Plots show median and 90% intervals (solid and dashed lines). The 90% prediction intervals for observations (lines with symbols) and predictions (lines) with 95% confidence intervals for prediction percentiles (gray shaded areas) are shown. From Anderson BJ, Holford NHG. Pediatr Anesth 2011; 21 (3): 222–237, with permission [16]

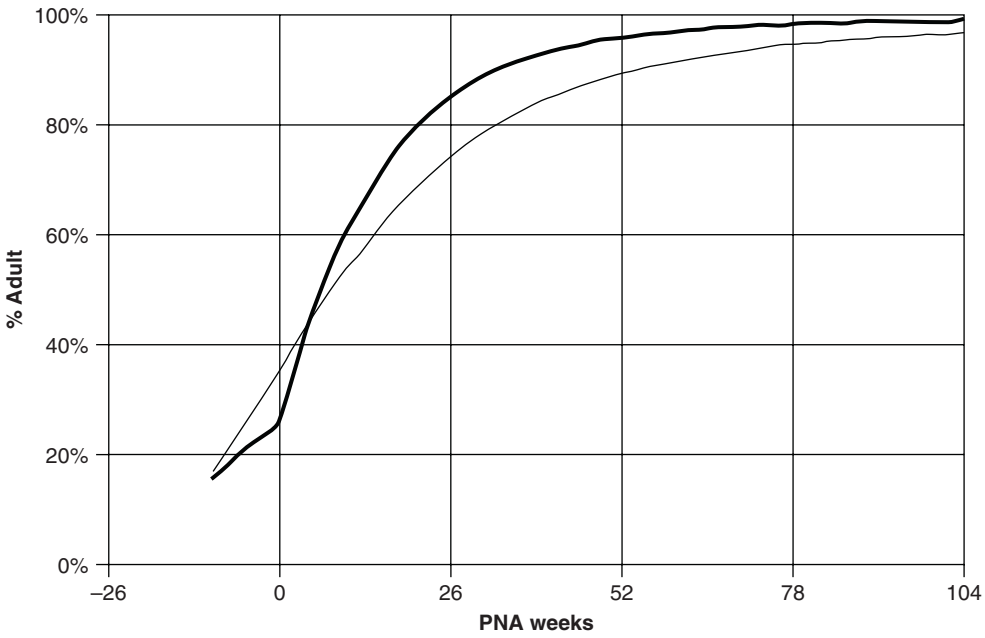


Fig. 3.4 Change in glomerular filtration rate (GFR) associated with maturation and birth at 40 weeks PMA. The maturation profile determined using PMA is shown as a black line. The effect of adding postnatal age (PNA) is shown as a grey line. Maturation is slower than anticipated before birth when PNA is unaccounted for and there is a slight increase of clearance maturation after birth. From Anderson BJ, Holford NHG. Pediatr Anesth 2011; 21 (3): 222–237, with permission [16]

asphyxia, organ damage, and illness. Postnatal changes in hepatic blood flow, protein binding, and/or biliary function may also alter drug elimination.

Organ Function

Changes associated with normal growth and development can be distinguished from pathological changes in organ function (OF) [6]. Pharmacokinetic parameters (P) can be described in an individual as the product of size (*Fsize*), maturation (MF), and organ function (OF) influences, where *Pstd* is the value in a standard size adult without pathological changes in organ function [6]:

$$P = Pstd \cdot Fsize \cdot MF \cdot OF$$

Organ function is typically depressed in the presence of disease. It may, however, also be increased by drugs. Phenobarbitone, a drug commonly given to neonates suffering from seizures, can induce enzyme activity of several enzyme systems responsible for clearance [27]: CYP1A2, CYP2C9, CYP2C19, CYP3A4, and UDP-glucuronosyltransferase (UGT) [28–30]. Phenobarbitone can increase the clearance of bilirubin in neonates through UGT induction [27], and of ketamine in older children [31], although no effect on ketamine in neonates has been reported.

Neonatal Pharmacokinetic Differences

Absorption

Anesthetic drugs are mainly administered through the intravenous and inhalational routes, although premedication and postoperative pain relief are commonly administered enterally. Drug absorption after oral administration in neonates is slower than in children due to delayed gastric emptying in the former (Fig. 3.5). Transgastric absorption may not reach adult rates until 6–8 months PNA [33, 34]. Congenital malformations (e.g., duodenal atresia), coadministration of drugs (e.g., opioids), and disease characteristics (e.g., necrotizing enterocolitis) may further affect the variability in drug absorption. Delayed gastric emptying and reduced clearance may dictate reduced doses and frequency of repeated drugs. For example, a mean steady-state target concentration of paracetamol greater than 10 mg/L at trough can be achieved by an oral dose of 25 mg/kg/day in preterm neonates at 30 weeks, 45 mg/kg/day at 34 weeks, and 60 mg/kg/day at 40 weeks PMA [32]. Because gastric emptying is slow in preterm neonates, dosing may only be required twice daily [32]. In contrast, the rectal administration of some drugs (e.g., thiopentone, methohexitone) results in more rapid absorption in neonates than in adults undergoing cardiac catheter study or radiological sedation. However, the interindividual variability in absorption and relative bioavailability may be more extensive compared with oral administration, rendering rectal administration less suitable for repeated administration [35].

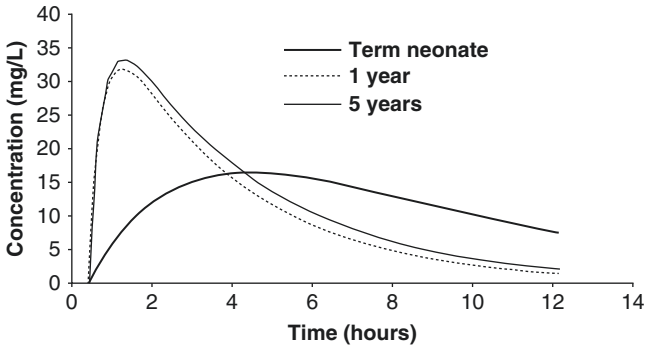


Fig. 3.5 Simulated mean predicted time-concentration profiles for a term neonate, a 1-year-old infant, and a 5-year old child given paracetamol elixir. The time to peak concentration is delayed in neonates due to slow gastric emptying and reduced clearance (from Anderson BJ et al. Anesthesiology 2002; 96:1336–45) [32]

The relatively greater skin surface area to body weight, increased cutaneous perfusion, and thinner stratum corneum in neonates increase systemic exposure of topical drugs (e.g., corticosteroids, local anesthetic creams, antiseptics). Neonates have a greater tendency to form methemoglobin because of reduced methemoglobin reductase activity compared with older children. Furthermore, fetal hemoglobin is more readily oxidized compared with adult hemoglobin. Combined with an increased transcutaneous absorption, these have resulted in a reluctance to reapply topical local anesthetics such as EMLA® (lidocaine-prilocaine) cream to neonates in this age group [36]. Similarly, cutaneous application of iodine antiseptics in neonates may result in transient hypothyroidism.

Drug administration and absorption through the nasal route in young children has become popular [37], but remains problematic in neonates. The recommended volume for delivery is 0.3 mL/kg in adults but only 0.1 mL/kg in small children and even less in neonates. This volume is easily exceeded for many commercially prepared drugs and spill over into the pharynx and ultimately to the gastrointestinal tract. An unknown fraction of the given dose will have delayed absorption and reduced bioavailability as a consequence of this gastrointestinal absorption.

The delivery of inhalational anesthetics is determined primarily by the alveolar ventilation to functional residual capacity (FRC) ratio. This ratio in neonates is greater than that in adults, primarily due to the increased metabolic demand for oxygen in neonates, which drives an increase in

alveolar ventilation. Consequently, the alveolar to inspired fractions, and, therefore, the blood to inspired partial pressure of inhalational anesthetics, reach equilibration more rapidly in neonates than in older children and adults [38]. The greater cardiac output and the greater fraction of the cardiac output distributed to vessel rich tissues (i.e., a clearance factor) and the reduced tissue/blood solubilities (i.e., a volume factor) further contribute to the more rapid wash-in of inhalational anesthetics in early life [39, 40].

Disease characteristics may also contribute to the variability in the absorption of inhalational anesthetics. Right-to-left shunts affect the wash-in of inhalational anesthetics to a greater extent than left-to-right shunts. Induction of anesthesia may be slowed by right-to-left shunting of blood in neonates suffering cyanotic congenital cardiac disease or intrapulmonary (right-to-left) conditions. This slowing is greatest with the least soluble anesthetics (e.g., nitrous oxide (N_2O), desflurane and to a lesser extent, sevoflurane). Left-to-right shunts usually have minimal impact on uptake, because the increase in cardiac output maintains systemic tissue perfusion at normal levels in the absence of heart failure.

Distribution

Distribution describes the movement from systemic circulation into various body compartments, tissues, and cells. Distribution is influenced by body composition, protein binding, hemodynamics (e.g., regional blood flow), and membrane permeability. Disease processes may also impact on the distribution of drugs.

Body Composition

Total body water and extracellular fluid (ECF) [41] decrease throughout gestation, the neonatal period, and childhood (Fig. 3.6), whereas the percent of body weight contributed by fat increases from 3% in a 1.5-kg preterm neonate to 12% in a full-term neonate and then doubles by 4–5 months PNA. These changes in the body composition substantively affect the volumes of distribution (V_d) of drugs. Polar drugs such as depolarizing and nondepolarizing neuromuscular-blocking drugs (NMBDs) distribute rapidly into the ECF but enter cells more slowly. Consequently, the initial doses of these drugs in neonates are greater than in children or adults.

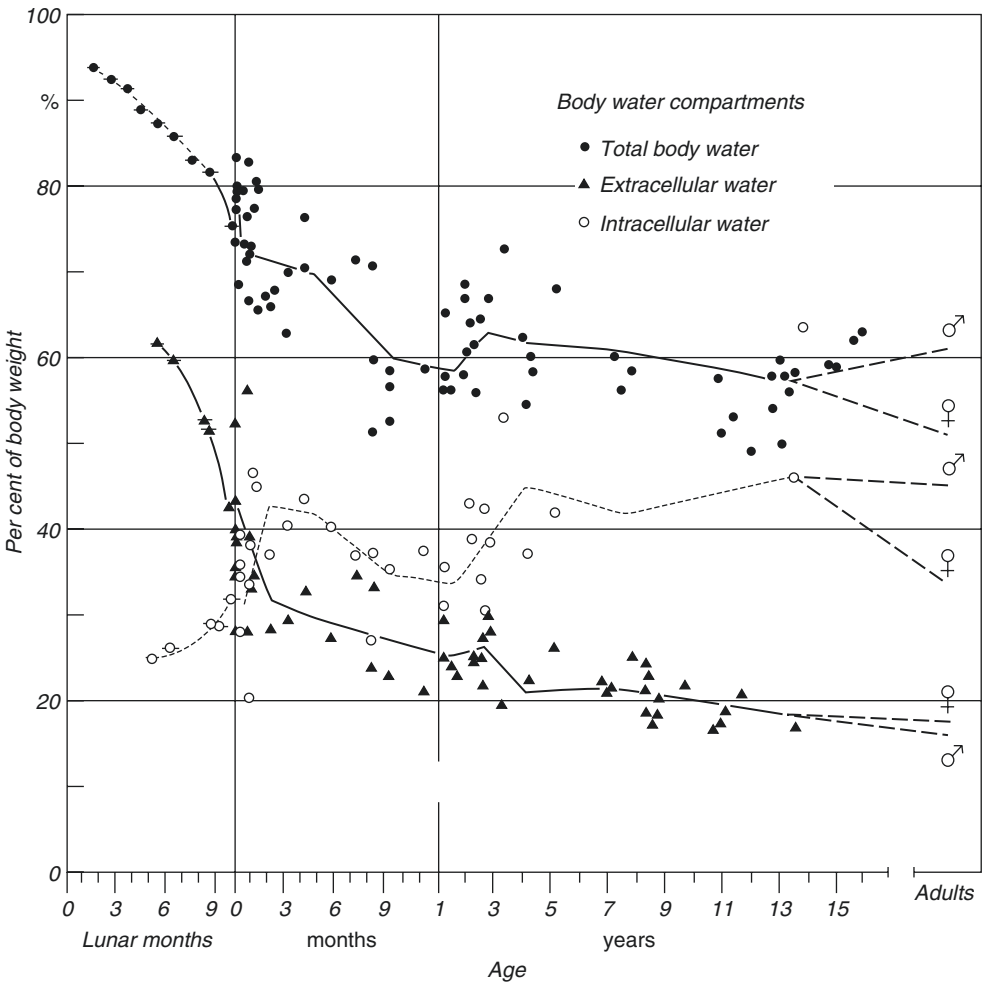


Fig. 3.6 Body water compartment changes during growth [41]

The V_d of lipid-soluble drugs in neonates may also be increased. At steady state, the V_d of fentanyl in neonates is 5.9 (SD 1.5) L/kg compared with 1.6 (SD 0.3) L/kg in adults [42]. This may explain the reduced frequency of respiratory depression after large doses of fentanyl, 10 μg/kg, in full-term neonates. However, high-dose therapy (50 μg/kg fentanyl) results in a prolonged effect in neonates due to the reduced clearance. In the case of propofol, the decreased plasma concentration after induction of anesthesia has been attributed to redistribution rather than rapid clearance. Neonates have less body fat and muscle content than older children; hence, less propofol is apportioned to these "deep" compartments. As a result, redistribution of propofol in the neonate is attenuated. Thus, repeat doses of propofol may accumulate in blood and brain tissue, the latter leading to delayed awakening.

Plasma Proteins

Albumin and alpha-1 acid glycoprotein (AAG) concentrations are reduced in neonates, albeit with a broad range (0.32–0.92 g/L), but reach adult concentrations by 6 months of age (Fig. 3.7) [43, 44]. AAG is an acute phase reactant that increases after surgical stress. This increases the total plasma concentrations for low to intermediate extraction drugs such as bupivacaine that bind to AAG [45]. The concentration of unbound bupivacaine, however, will not change, because the clearance of unbound bupivacaine depends only on the intrinsic metabolizing capacity of the liver. Any increase in unbound concentrations during long-term epidural infusion, for example, is attributable to a reduced clearance rather than a decrease in the AAG concentration [46]. Total bupivacaine concentrations increase during the first 24 h after surgery in neonates who are receiving a continuous epidural infusion of bupivacaine; unbound bupivacaine concentrations, however, may not increase; any accumulation depends on clearance. The increase in total bupivacaine is attributable in part to an increase in AAG. This increase in total bupivacaine, combined with reports of seizures in infants with epidural infusions of bupivacaine, has led to recommendations to stop the epidural infusion at 24 h or change the local anesthetic used. However, it is the concentration of unbound bupivacaine that confers its CNS effects and this, in turn, is determined by the clearance of the unbound bupivacaine. Clearance, the pivotal variable in the elimination of unbound bupivacaine, is reduced in neonates. Furthermore, clearance shows large interindividual variability, which means that unbound bupivacaine concentrations may increase steadily in some individuals with very low clearance. The lack of knowledge of the clearance of bupivacaine in each neonate precludes pronouncing a safe duration of epidural infusions of bupivacaine for all neonates [47].

Plasma concentrations of albumin are least in preterm neonates but increase steadily, approximating adult values by 5 months of PNA. Binding capacity approaches adult values by 1 year of age. Furthermore, free fatty acids and unconjugated bilirubin compete with acidic drugs (e.g., ibuprofen, ceftriaxone) for albumin binding. The induction dose of thiopentone in neonates is less than it is in children. This may be related to the decreased binding of thiopentone to plasma albumin; 13% of the drug is unbound in neonates compared with 7% in adults [48].

Regional Blood Flows

The initial phase of distribution reflects the magnitude of regional blood flow. Consequently, the brain, heart, and liver, which receive the largest fraction of cardiac output, are first exposed. Drugs are then redistributed to other relatively well-perfused tissues, such as skeletal muscle. There is a much slower tertiary distribution to relatively underperfused tissues of the body that is noted with long-term drug infu-

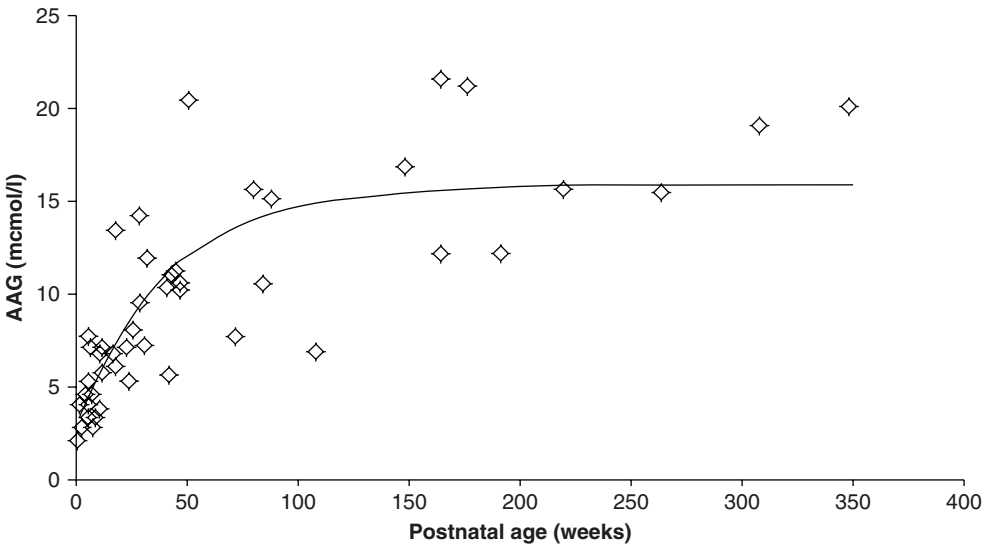


Fig. 3.7 Alpha-1 acid glycoproyein changes with age. Adapted from Booker P. Br J Anaesth 1996;76:365–8

sions. In addition to perinatal circulatory changes (e.g., ductus venosus, ductus arteriosus), there are maturational differences in relative organ mass (Fig. 3.8) and regional blood flow, while a symptomatic patent ductus arteriosus may also result in differences in distribution. Blood flow to the kidney and brain, when expressed as a fraction of the cardiac output, increases with age, whereas flow to the liver decreases through the neonatal period [49]. Cerebral and hepatic mass as fractions of the total body weight in the infant is much greater than in the adult [50]. Although the onset times of drugs in neonates are generally more rapid than in adults (a size effect), the reduced cardiac output and cerebral perfusion in neonates may delay the onset of action of intravenous drugs, an effect that may be offset, in part, by the reduced protein binding of those drugs in neonates. As a result, the onset time for each drug must be investigated in neonates to establish the net effect of these competing factors. Offset time is also delayed, because redistribution to well-perfused and deep underperfused tissues is more limited.

Blood–Brain Barrier (BBB)

The blood–brain barrier (BBB) is a network of tight junctions that restricts paracellular diffusion of compounds

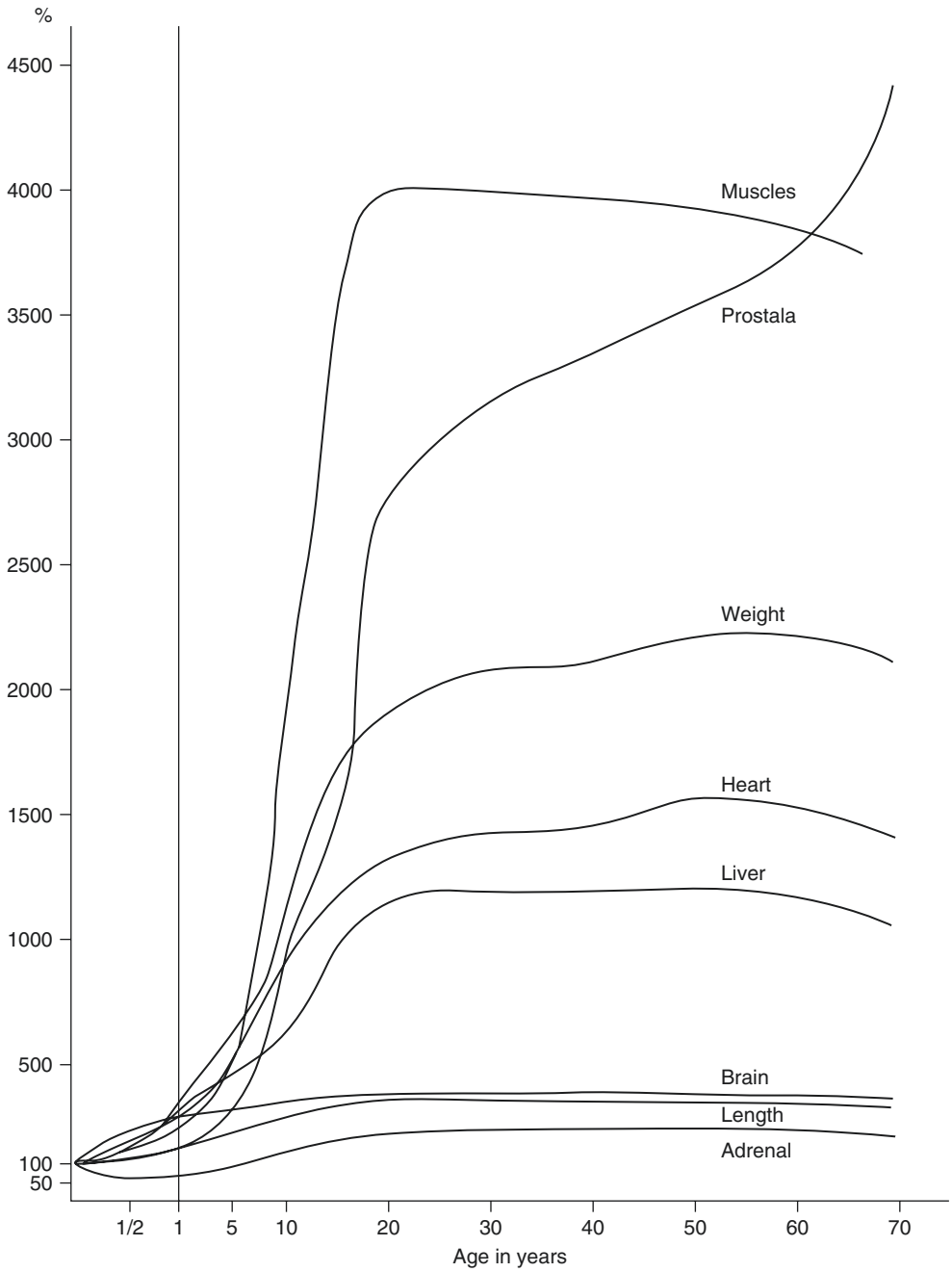


Fig. 3.8 The increase in weight of different organs expressed as a percent of their weight in the newborn. From Friis-Hansen B. Pediatrics 1971; 47, Suppl 2: 264–274

between blood and brain tissue. Confusion over the importance of this barrier in the neonate may be attributed to early studies that reported respiratory depression after morphine and meperidine administration [51]. Early investigations reported that the respiratory depression after morphine was greater than that after meperidine. This difference was attributed to greater brain concentrations of morphine, because the BBB in the neonate was poorly developed [51]. It was postulated that BBB permeability to water-soluble drugs, such as morphine, decreases with maturation [51]. However, the respiratory depression observed after morphine in neonates could have been explained by age-related pharmacokinetic differences. For example, the V_d of morphine in term neonates 1–4 days (1.3 L/kg) is less than that in infants 8–60 days of age (1.8 L/kg) and adults (2.8 L/kg) [52]. Consequently, the initial concentrations of morphine in neonates may be greater than those in adults, resulting in more pronounced respiratory depression in the former. However, respiratory depression, measured by carbon dioxide response curves or by arterial oxygen tension, is similar in neonates, infants, and children from 2 to 570 days of age at the same morphine blood concentration [53]. The BBB theory in this particular circumstance lacks strong evidence. It is more likely that the increased respiratory depression after morphine in neonates is explained by age-related pharmacokinetic differences than BBB permeability or other factors.

The BBB however may impact drug responses in other ways. Small molecules are thought to access fetal and neonatal brain tissue more readily than adult brain tissue [54]. BBB function improves gradually, possibly reaching maturity by full-term age [54]. Kernicterus, for example, is more common in preterm neonates than in full-term neonates. In contrast to drugs bound to plasma proteins, unbound lipophilic drugs passively diffuse across the BBB, equilibrating very quickly. This may contribute to the propensity of bupivacaine for inducing seizures in neonates. Decreased protein binding, as in the neonate, results in a greater proportion of unbound drug that is available for passive diffusion into the brain.

In addition to passive diffusion, there are specific transport systems that mediate active transport. Pathological CNS conditions can cause BBB breakdown and alter these transport systems. Fentanyl is actively transported across the BBB by a saturable ATP-dependent process, while ATP-binding cassette proteins such as P-glycoprotein actively efflux opioids such as fentanyl and morphine from the brain [55, 56]. P-glycoprotein modulation significantly influences opioid brain distribution and onset time, magnitude, and duration of analgesic response [57]. Modulation may occur during disease processes, fever, or in the presence of other drugs (e.g., verapamil, magnesium) [55]. Genetic polymorphisms that affect P-glycoprotein-related genes may explain differences in CNS-active drug sensitivity [56, 58].

Elimination

The main routes by which drugs and their metabolites are eliminated from the body are the hepatobiliary system, the kidneys, and the lungs. The liver is the primary organ for clearance of most drugs, although the lungs have a major role for inhalational anesthetics. Drug-metabolizing enzymes are generally divided into phase I and phase II reactions. Phase I reactions are nonsynthetic reactions like oxidation, reduction, and hydrolysis. The most important group of enzymes involved in phase I processes are the cytochrome P450 (CYP) iso-enzymes. Phase II reactions convert lipid-soluble drugs to water-soluble compounds, for example, uridinediphosphate-glucuronosyltransferase (UGT). Metabolism may transform a prodrug into an active drug (e.g., codeine to morphine by CYP2D6, propacetamol to paracetamol by esterase, morphine to morphine-6-glucuronide by UGT2B7) or a toxic compound (halothane to trifluoroacetyl chloride by CYP2E1 causing halothane hepatitis).

Hepatic Metabolic Clearance

Constitutional, environmental, and genetic factors all contribute to the variability in clearance, but in the young neonate, age is the dominant covariate. Most CYP iso-enzymes, except for CYP3A7, have small phenotypic activity until birth [59, 60]. CYP2E1 activity surges after birth [61], CYP2D6 becomes detectable soon thereafter, CYP3A4 and CYP2C (Fig. 3.9) are detectable during the first week postnatally, whereas CYP1A2 is the last to appear [62]. Neonates depend on the immature CYP3A4 for levobupivacaine or midazolam clearance and on CYP1A2 for ropivacaine clearance, dictating reduced epidural infusion rates in this age group [1, 63, 64]. Formation of the M1 metabolite of trama-

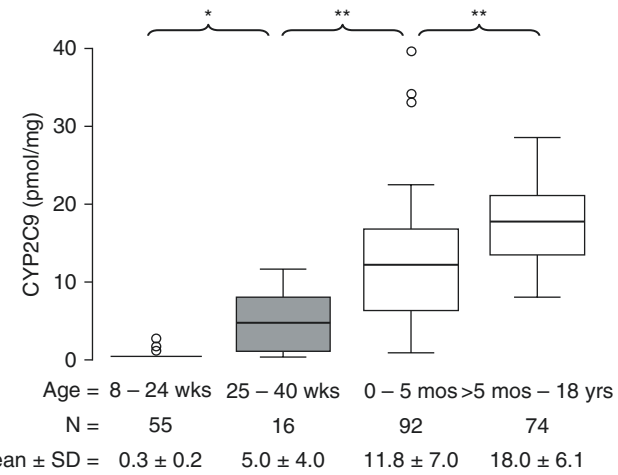


Fig. 3.9 Developmental expression of human hepatic CYP2C9 enzyme. [60]

dol, a reflection of CYP2D6 activity [65], appears rapidly at term and reaches 84% of mature values by 44 weeks PMA.

Pharmacogenomics (PG) investigates variations of DNA and RNA characteristics related to drug response that incorporates both PK and PD. Large interindividual PK variability depends to a large extent on polymorphisms of the genes that encode for metabolic enzymes [66]. The effect of genetic variability on plasma cholinesterase activity and its effect on the termination of action of succinylcholine is a well-known example and the first polymorphism described in anesthesia. Another example is the CYP2D6 single nuclear polymorphism (SNP), inherited as an autosomal-recessive trait that may result in poor analgesia from codeine, because the active metabolite morphine is not formed. Both PMA and CYP2D6 activity explain the interindividual variability in tramadol metabolism (Fig. 3.10). The interplay between maturation of tramadol clearance, M1 metabolite formation, and maturing GFR on M1 concentration (and subsequent analgesia) is shown in Fig. 3.11.

Some phase II iso-enyzmes are mature in full-term neonates at birth (sulfate conjugation), whereas others are not (acetylation, glycination, glucuronidation) [68]. Glucuronidation is important in the metabolic clearance of drugs (paracetamol, morphine, propofol) frequently administered by anesthesiologists. Allometric body-size scaling complemented by maturation models [12, 69] has unraveled the effects of maturation of the pharmacology of morphine [70, 71] and paracetamol [72, 73]. Both drugs are cleared by specific isoforms (UGT1A6 and UGT2B7). In both instances, clearance is immature in the preterm 24 week PMA neonate and matures to reach adult rates by the end of the first year of life (Fig. 3.12). Dexmedetomidine is also cleared predominantly by the UGT system and has a similar maturation profile [74].

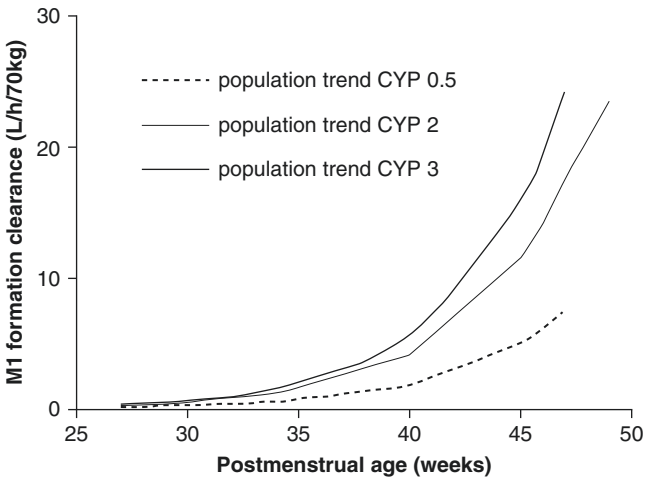


Fig. 3.10 Tramadol M1 metabolite formation clearance (CYP2D6) increases with postmenstrual age. Rate of increase varies with genotype expression. Adapted from Allegaert K. et al. [65]

Glucuronidation is the major metabolic pathway for propofol. This pathway is immature in neonates, although multiple CYP iso-enzymes (CYP2B6, CYP2C9, CYP2A6) also contribute to its metabolism and cause a more rapid maturation profile than expected from glucuronidation alone [26] (Fig. 3.12). Urine collections after intravenous boluses of propofol in neonates (PNA 11 days, PMA 38 weeks) support this contention. Urinary metabolites included both propofol glucuronide and 1- and 4-quinol glucuronide in a ratio of 1:2. Hydroxylation to quinol metabolites was active in these neonates [77], contributing to the rapid increase in clearance at this age that is faster than that reported for glucuronide conjugation alone (e.g., paracetamol, morphine).

Disease characteristics also contribute to the variability in UGT-related clearance. Maturation of morphine clearance occurs more quickly in infants undergoing noncardiac surgery compared with those after cardiac surgery [78]. Neonates requiring extracorporeal membrane oxygenation [79] or positive pressure ventilation [71, 80] also have reduced clearance (Fig. 3.13). Similarly, the clearance of propofol is reduced after cardiac surgery in children [81].

Extrahepatic Routes of Metabolic Clearance

Many drugs undergo metabolic clearance at extrahepatic sites. Remifentanil and atracurium are degraded by nonspecific esterases in tissues and erythrocytes and these processes appear mature at birth, even in preterm neonates [24]. Clearance, expressed per kilogram, is increased in younger children [82–86], and is likely attributable to size, because clearance is similar when scaled to a 70 kg person using allometry [82]. Succinylcholine clearance is also increased in neonates [87, 88] suggesting butyryl-cholinesterase activity is mature at birth.

Pulmonary Elimination

The factors that determine anesthetic absorption through the lung (alveolar ventilation, FRC, cardiac output, solubility) also contribute to elimination kinetics. We might anticipate more rapid washout in neonates for any given duration of anesthesia because of the greater alveolar ventilation to FRC ratio, greater fraction of cardiac output perfusing vessel-rich tissues, reduced solubility in blood and tissues, and reduced distribution to fat and muscle content. Furthermore, younger age (as in the neonate) speeds the elimination of more soluble inhalational anesthetic such as halothane to a greater extent than the less soluble anesthetic, desflurane and sevoflurane primarily. Halothane, and to a far lesser extent isoflurane (1.5%) and sevoflurane (5%), undergoes hepatic metabolism. Halothane is reported to undergo as much as 20–25% metabolism, but at typical anesthetizing concentrations, hepatic halothane removal is extremely small [89].

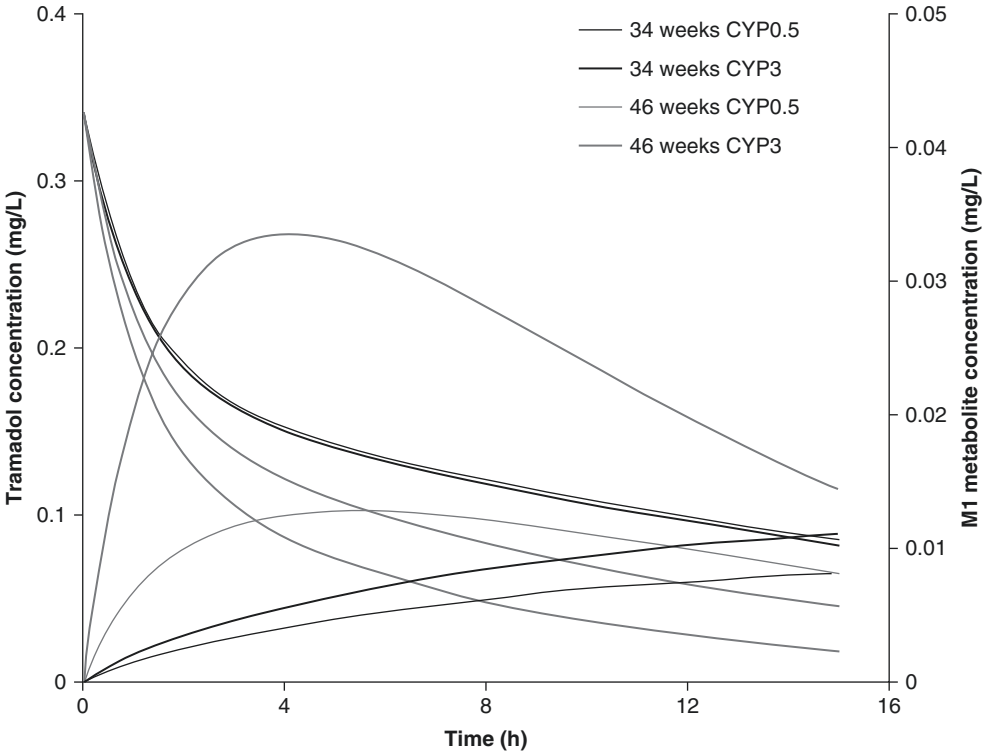


Fig. 3.11 Time-concentration profiles for tramadol and the M1 metabolite in neonates. CYP2D6 activity has been assigned a score of 0–3. Clearance of the parent drug is reduced in the 34 week PMA neonate compared to the 46 week PMA neonate and CYP activity has little impact on profiles. At 46 weeks, both total clearance and CYP2D6 activity has increased, resulting in distinct profiles. The M1 metabolite is cleared by renal function and the rapid maturation of glomerular filtration rate around 40 weeks PMA has impact on the M1 metabolite profile, resulting in a peak concentration and subsequent decrease. Adapted from Allegaert K. et al. [9]

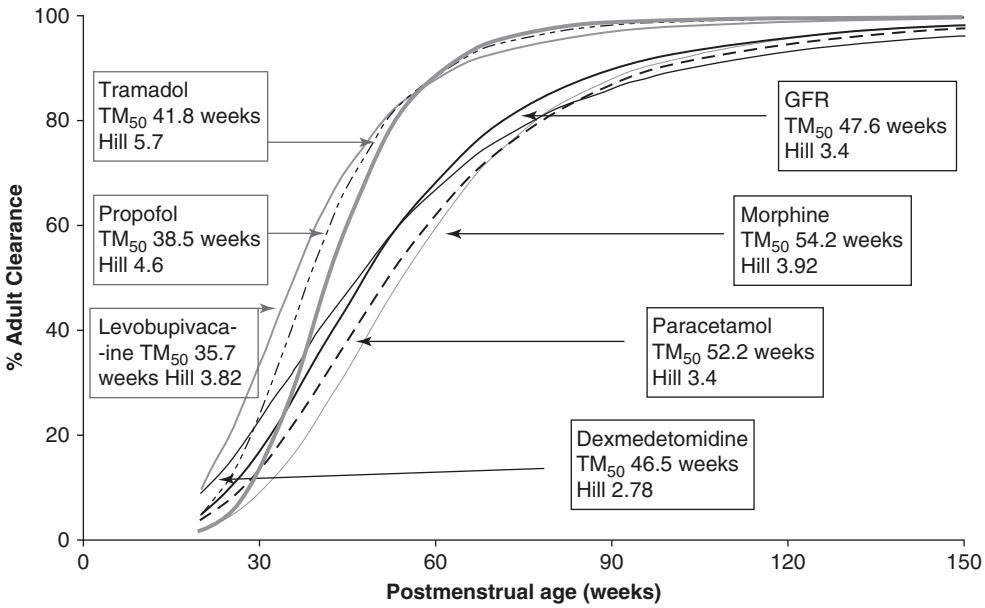


Fig. 3.12 Clearance maturation, expressed as a percentage of mature clearance, of drugs where glucuronide conjugation (paracetamol, morphine, dexmedetomidine) plays a major role. These profiles are closely aligned with glomerular filtration rate (GFR). In contrast, cytochrome P450 isoenzymes also contribute to propofol metabolism and cause a faster maturation profile than expected from glucuronide conjugation alone. Tramadol clearance maturation (Phase I, CYP2D6, CYP3A) is also rapid. Maturation parameter estimates were taken from Refs. [64, 65, 69, 71, 74–76]

Renal Elimination

Renal elimination of drugs and their metabolites occurs primarily by two processes: glomerular filtration and tubular secretion. Glomerular filtration rate (GFR) at 25 weeks is only 10% that of the adult value, 35% at term, and 90% at 1 year of age (Fig. 3.12) [75]. Aminoglycosides are almost exclusively cleared by renal elimination and maintenance dose is predicted by PMA because it predicts the time course of renal maturation [90]. The kidney is also capable of metabolizing drugs; CYP2E1, which metabolizes ether inhalational anesthetics, is active in the kidney. The very presence of CYP2E1 in the kidney is responsible for the degradation of ether inhalational anesthetics and the release of nephrotoxic inorganic fluoride [91].

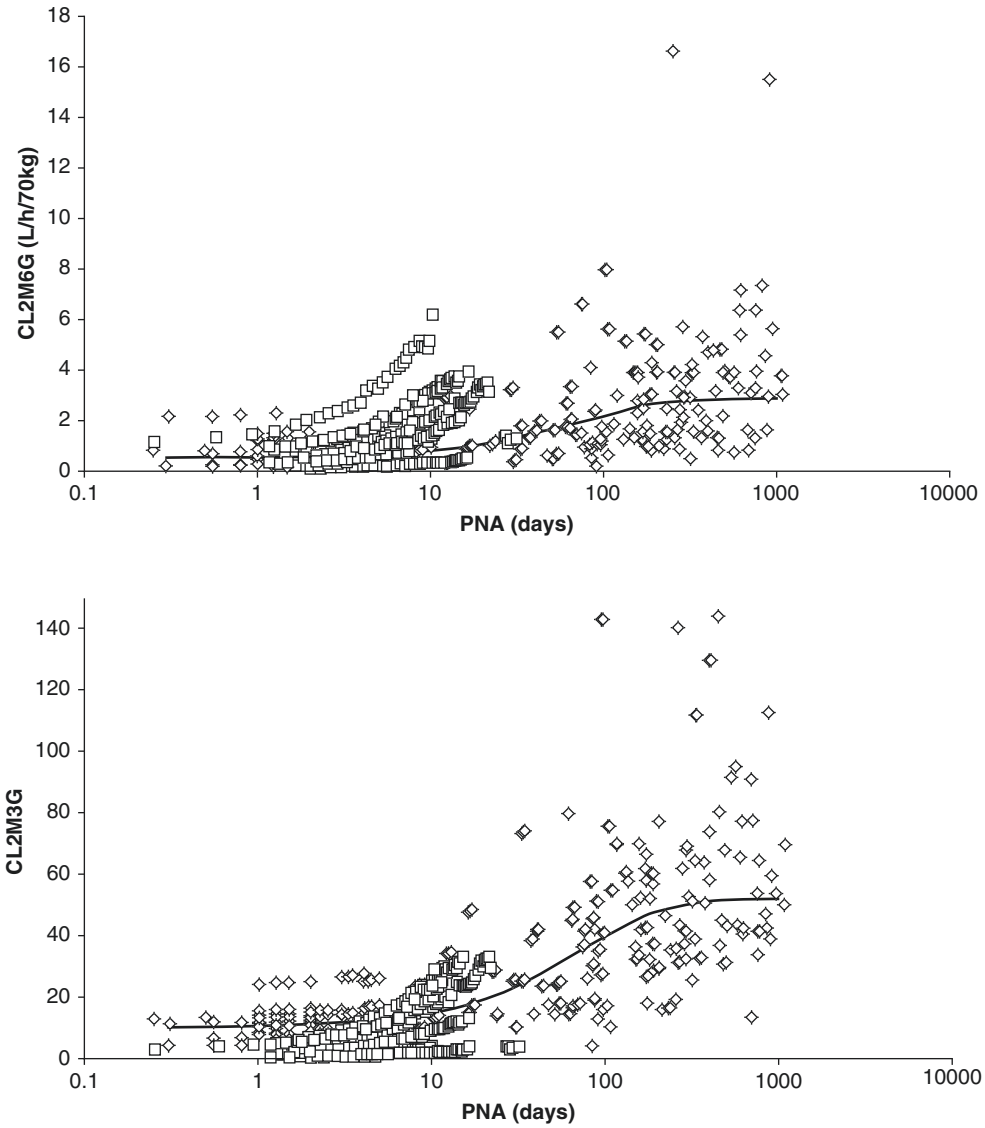


Fig. 3.13 Morphine clearance in neonates during ECMO. The maturation of clearance to morphine-6-glucuronide (CL2M6G) and morphine-3-glucuronide (CL2M3G) is faster (open squares) in children requiring ECMO than those not requiring ECMO (open triangles) From Peters JWB, Anderson BJ, Simons SHP, Uges DRA, Tibboel D. Morphine metabolite pharmacokinetics during venoarterial ECMO in neonates. Clinical Pharmacokinet 2006; 45: 705–714

Immaturity of the clearance pathways can be used to our advantage when managing apnea after anesthesia in the preterm neonate. N_7-methylation of theophylline to produce caffeine is well developed in the neonate, whereas oxidative demethylation (CYP1A2) responsible for caffeine metabolism is deficient. Theophylline is effective for the management of postoperative apnea in the preterm neonate, in part because it is a prodrug of caffeine, which is effective in controlling apnea in this age group and can only be cleared slowly by the immature kidney [92].

Milrinone, an inodilator, is used increasingly in children after congenital cardiac surgery. Renal clearance is the primary route of elimination. A clearance of 9 L/h/70 kg is reported in adults with congestive heart failure, and we might anticipate that clearance in preterm neonates is reduced to 10% of this rate, because renal function is correspondingly immature in this cohort. This has been confirmed in 26-week PMA preterm infants whose milrinone clearance was 0.96 L/h/70 kg [93]. Similarly, the clearance of the neuromuscular-blocking drug NMBD, d-tubocurare, can be directly correlated with GFR [94]. Some drugs such as the nonsteroidal anti-inflammatory agents (NSAIDs) may compromise renal clearance in early life: ibuprofen reduces GFR by 20% in preterm neonates, independent of gestational age [95, 96].

Neonatal Pharmacodynamic Differences

Children's responses to drugs have much in common with the responses in adults once developmental PK aspects are considered [97]. The perception that drug effects differ in children arises, because these drugs have not been adequately studied in pediatric populations who have size and age-

related effects as well as different diseases. Neonates, however, often have altered pharmacodynamics as well.

The minimum alveolar concentration (MAC) is commonly used to express the potency of inhalational anesthetics. The MAC values for most anesthetics in neonates are less than those in older infants (Fig. 3.14) [39]. The MAC of isoflurane in preterm neonates <32 weeks gestation is 1.28% (SD 0.17), and in preterm neonates 32–37 weeks gestation, 1.41% (SD 0.18), which in turn is less than in full-term neonates [98]. Similarly, the MAC of halothane in full-term neonates (0.87% SEM 0.03) is less than that in infants 1–6 months of age (1.20% SEM), but the decrease in blood pressure and the incidence of hypotension in neonates and infants at approximately 1 MAC of halothane are similar [99].

Assessment of sedation using modified electroencephalographic signals in neonates remains difficult. Three methods (Neonatal Pain, Agitation and Sedation Scale, amplitude-integrated Electroencephalogram, and Bispectral Index), and their combination, have been used to detect different levels of sedation in neonates. Although none of the three methods alone were satisfactory to discriminate between degrees of sedation, the combination was effective in distinguishing between light and deep sedation [100]. The processed EEG (spectral edge frequency, BIS, entropy) may not be reliable in neonates and infants, but the EEG waveforms and changes in the dimensionless number that is its output have permitted some interpretation [101]. Age-dependent EEG changes with sevoflurane anesthesia reflect cerebral maturation and, in particular, neuronal myelination [102–105]. Clinical signs rather than processed EEG are currently required to assess the depth of anesthesia in neonates and infants.

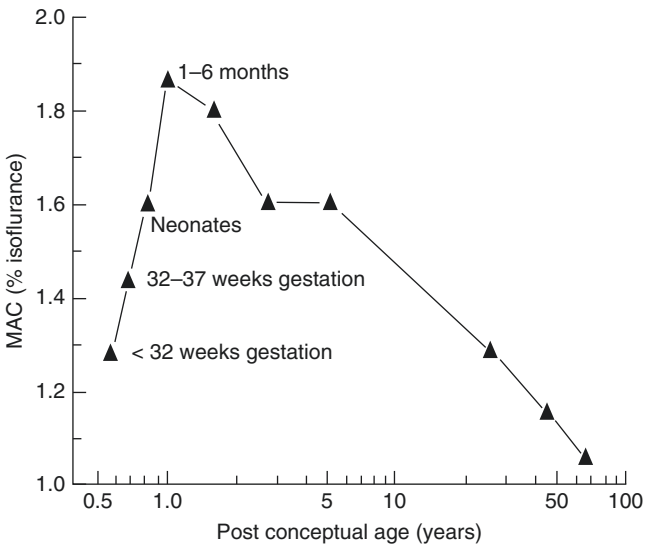


Fig. 3.14 Effect of age on the minimum alveolar concentration (MAC) of isoflurane. MAC increases as age decreases, reaching a zenith in infants 1–6 months of age and decreases thereafter as age decreases to 24 weeks gestation [98].

Changes in regional blood flow may influence the amount of drug that reaches the brain. Inhalational anesthetics are believed to affect the CNS via gamma-aminobutyric acid ($GABA_A$) receptors. Receptor numbers or developmental shifts in the regulation of chloride transporters in the brain may change with age, altering the response to these anesthetics. Midazolam acts on the same receptors. Data from rodents from birth to PNA 40 days have shown developmental PD changes for sedation that mimic those observed in human childhood [106]. Such models offer potential to improve our understanding of developmental pharmacology [107].

Neonates demonstrate an increased sensitivity to the effects of neuromuscular blocking drugs [94]. The reason for this sensitivity is unknown, but the finding is consistent with the observation that there is a three-fold reduction in the release of acetylcholine from the infant compared with the phrenic nerve in the adult rat [108, 109]. Reduced clearance and increased sensitivity prolong the duration of neuromuscular effect. Similarly, the smaller concentrations of epsilon-aminocaproic acid required to inhibit fibrinolysis may be attributed to the immature coagulation system in neonates [110].

The duration of regional block with amide local anesthetic agents in infants is reduced compared with older children. Moreover, infants require a larger weight scaled dose to achieve a similar dermatomal level when local anesthetics are given by subarachnoid block. This may in part be due to reduced myelination in infants, increased spacing of nodes of Ranvier, and the length of nerve exposed.

Expression of intestinal motilin receptors and the modulation of antral contractions in neonates depend on age. Prokinetic agents may not be useful in extremely preterm neonates, useful only in part in older preterm infants, but very useful in full-term infants. Similarly, bronchodilators are ineffective in neonates because of the paucity of bronchial smooth muscle that can cause bronchospasm.

Cardiac calcium stores in the endoplasmic reticulum are reduced in the neonatal heart because of immaturity. Exogenous calcium has a greater impact on contractility in this age group than in older children or adults. Conversely, calcium channel–blocking drugs (e.g., verapamil) can cause life-threatening bradycardia and hypotension [111]. Catecholamine release and the response to vasoactive drugs vary with age. These pharmacodynamic differences are based in part upon developmental changes in myocardial structure, cardiac innervation, and adrenergic receptor function. For example, the immature myocardium has fewer contractile elements and therefore a decreased ability to increase contractility; it also responds poorly to standard techniques of manipulating preload [112]. Dopaminergic receptors are present in the pulmonary vasculature and may be responsible for mediating pulmonary vasoconstriction in preterm neonates. However, systemic vasoconstriction is greater than that observed in the pulmonary circulation and

this differential response contributes to the use of dopamine in neonates with known pulmonary hypertension after cardiac surgery. Neonates have underdeveloped sympathetic innervation and reduced stores of norepinephrine. Signs of cardiovascular α-receptor stimulation may occur at lower doses than β-receptor stimulation, because β-receptor maturation lags behind α-receptor maturation during the development of the adrenergic system [113]. The preterm neonate has immature metabolic and elimination pathways, leading to increased dopamine concentrations after prolonged infusions [113–116]. These maturational changes in PK and PD may contribute to dopamine's continued popularity in the neonatal nursery, while its popularity wanes in the adult population.

Pharmacodynamic Measures

In general, outcome measures are more difficult to assess in neonates than in children or adults. The common effects measured in anesthesia are circulatory and respiratory depression, neuromuscular blockade, depth of anesthesia, and sedation or pain. Circulatory responses may be assessed using heart rate and blood pressure, although more detailed analyses require echocardiography and electrophysiology of the conduction systems. Similar respiratory responses may be recorded in terms of respiratory rate and gas exchange (oximetry and capnometry), but more sophisticated effects require CO_2 response curves and compliance changes. Electromyography response of the adductor pollicis is a consistent metric to investigate neuromuscular blockade in both neonates and adults. Differences are minor, for example, neonates tolerate repetitive stimulations for briefer periods than older children, because the former have limited acetylcholine reserves. Assessment of outcome variables, however, becomes more difficult when the depth of anesthesia, sedation, and pain in neonates are considered.

A common metric to assess the depth of anesthesia is the electroencephalogram (EEG) or a modification of detected EEG signals (spectral edge frequency, Bispectral index, entropy). Physiological studies in adults and children indicate that EEG-derived anesthesia depth monitors provide an imprecise and drug-dependent measure of arousal. They can be used as guides for anesthesia and have improved outcomes in adults. In older children, the physiology, anatomy, and clinical observations indicate the performance of the monitors may be similar to that in adults. However, the depth of anesthesia (based on the BIS) after ketamine is inconsistent. In the case of sevoflurane, the BIS in children paradoxically increases when the end-tidal concentrations increase beyond 3% [117]. In infants, the use of these monitors cannot yet be supported in theory or in practice [118, 119]. Both outside and during anesthesia, the EEG in infants is fundamentally different from that in older children; there remains a need for specific neonate-derived algorithms if EEG-derived anesthesia depth monitors are to be used routinely in neonates [120, 121].

The existence of a large number of sedation or pain scales should not suggest that all of the difficulties in assessing pain in the neonate have been solved. Most scores are validated for the acute, procedural setting and perform less reliably for subacute or chronic pain or stress. Scoring systems seldom take into account the limited capacity of the more immature infants to mount a consistent behavioral and physiological response to pain. Validation is based on the assessment of intra- and interindividual variability and correlations with neuroendocrine markers of stress or pain. Future research may provide us with objective tools to quantify pain and sedation but will have to take maturational aspects of the neonate into account.

Induction Agents

Intravenous induction agents exert their anesthetic effects by achieving adequate cerebral concentrations. Termination of a drug's effect may be attributed to redistribution rather than rapid clearance. With less body fat and muscle, less drug is apportioned to these "deep" compartments in neonates. Accordingly, a delay in emergence from anesthesia in neonates can be attributed directly to greater concentrations of anesthetic in the brain that result from reduced redistribution compared with older children.

Propofol

Mechanism

The hypnotic actions of propofol result from its interaction with the $GABA_A$ receptor [122, 123].

Pharmacodynamics

Integrated PK-PD studies in neonates are lacking, partly due to a lack of consistent effect measures. Consequently, the target concentration for anesthesia in neonates is unknown. The equilibration half-time ($T_{1/2}keo$) for the effect compartment is unknown, but is assumed to be less than the 3 min described in adults [124, 125]; $T_{1/2}keo$ becomes smaller as age decreases [126] and relates to weight with an allometric exponent of 1/4 [127]. Reduced $GABA_A$ receptor numbers in the neonatal brain may contribute to a reduced target concentration, but this hypothesis remains untested. A circadian night rhythm effect has been noted in an investigation of propofol sedation in infants after major craniofacial surgery [128], but such an effect is unlikely in neonates who do not have established day/night sleep cycles.

A target propofol concentration of 2–3 mg/L is commonly sought for sedation in children, whereas 4–6 mg/L is used for anesthesia. Both the loss and return of consciousness occur at similar target effect-site propofol concentrations (2.0 SD 0.9 mg/L vs. 1.8 SD 0.7 mg/L) in adults [129] and a "wake-up" concentration of 1.8 mg/L in children [130]. However, PKPD relationships in neonates are rarely described because of difficulties in interpreting effect measures (e.g., EEG signals). Propofol infusion rates for infants have been suggested [131]. Those regimens were determined by adapting an adult dosage scheme to the requirements of the younger population. The total number and time of administration of boluses and time to awakening were registered and used as criteria to adjust the dosage scheme. Predicted infusion rates are large (e.g., 24 mg/kg/h for the first 10 min in neonates) and should be used cautiously. Delayed awakening, hypotension, and an increased incidence of bradycardia were reported in neonates and infants at this rate [131].

Pharmacokinetics

Propofol is metabolized in the liver with an extraction ratio of approximately 0.9. Clearance is limited by the hepatic blood flow and reduced in children in low cardiac output states [81]. Clearance is affected primarily by UGT1A9 with contributions from CYP2B6, CYP2C9, and CYP2A6 isoenzymes resulting in a more rapid maturation profile than expected from glucuronide conjugation alone (Fig. 3.12).

Although propofol is widely used for target controlled infusion (TCI) anesthesia in children, commonly used TCI data sets [125, 131–134] have only investigated propofol PK in children beyond infancy. In an effort to link neonatal data with those from children [76], Allegaert used allometry and the Hill equation [69] to suggest a maturation half-time of 44 weeks and a Hill coefficient of 4.9 [135]. Clearance at 28 weeks gestation is only 10% of the mature value (1.83 L/min/70 kg) and at term, it remains reduced, at only 38% of the mature value. A full-term neonate achieves 90% of the adult clearance by 30 weeks PMA. Although PMA is the major descriptor of maturation, it is possible that PNA may also contribute to the maturation of propofol clearance, increasing the clearance beyond that predicted by PMA [26]. Further longitudinal studies that examine individual neonates as they grow are required to clarify this aspect of maturation.

Adverse Effects

Propofol is used for tracheal intubation by neonatologists [136, 137] and anaesthesiologists [138, 139]. Propofol doses of 2–3 mg/kg have been reported for intubation [139–141], although caution should be advocated in the early postnatal period during which a transient return to fetal circulation is possible ("flip-flop" phenomenon) due to reduced systemic vascular resistance concomitant with increased pulmonary resistance (associated with hypoxemia and acidosis) [142, 143]. Profound low cardiac output state, together with profound oxygen desaturation, has been reported in several neonates that were refractory to usual resuscitation measures including most inotropes [144]. Additionally, hypotension of 30 min duration has been reported in preterm neonates given propofol 3 mg/kg for procedural sedation in a neonatal intensive care unit [145], although the severity of the hypotension was similar to that reported after inhalational anesthetics at 1 MAC [144]. Other adverse effects (bradycardia, propofol infusion syndrome, respiratory depression, immune function) are poorly documented in neonates and require further investigation. Neonates can experience pain with an injection of propofol; some recommend IV lidocaine to ameliorate this effect.

Thiopentone

Mechanism

Thiopentone is an analog of pentobarbitone. The greater lipid solubility of thiopentone is achieved by substituting a sulfur atom in place of an oxygen atom on the barbiturate acid ring [146]. Greater penetration of the BBB has been described in neonatal compared with older animals, possibly attributable to the greater blood–brain flow in the former [147]. The most likely mechanism of action of thiopentone is via binding to $GABA_A$ receptors, which increases the duration of GABA-activated chloride opening.

Pharmacodynamics

The ED_{50} of thiopentone varies with age: 3.4 mg/kg in neonates, 6.3 mg/kg in infants, 3.9 mg/kg in children aged 1–4 years, 4.5 mg/kg in children 4–7 years, 4.3 mg/kg in children 7–12 years, and 4.1 mg/kg in adolescents aged 12–16 years [148, 149]. The reduced dose requirements in neonates may be explained by altered PK, PD, or a combination of the two. The effect-site concentration of thiopentone for induction of anesthesia in neonates may be less than that in infants, because the neonate has relatively immature cerebral cortical function, rudimentary dendritic arborizations, and relatively few synapses [150]. However, integrated PKPD studies with thiopentone in neonates have not been performed to confirm this notion [151]. The plasma concentration (EC_{50}) of thiopentone required for induction of anesthesia in adults based on the EEG is 17.9 mcg/mL; comparable data in neonates are lacking [152]. The $T_{1/2}keo$ in adults is 0.6 min [152], but there are no estimates in neonates. Children aged 13–68 months given rectal thiopentone (44 mg/kg) 45 min before surgery were either asleep or adequately sedated with plasma concentrations in excess of 2.8 mg/kg [153].

Pharmacokinetics

Peak concentrations of thiopentone in the brain and other well-perfused organs are achieved within one circulation time. Recovery results from redistribution. Reported pharmacokinetic parameter estimates have been derived from infusions administered for seizure control in neonates suffering hypoxic-ischemic insults. Clearance estimates in neonates range from 66 to 320 mL/h/kg with a volume of distribution at steady state (Vss) of 3.6–5.4 L/kg [154–157]. Interindividual variability was considerable [151]. While most clearance estimates are less than those in adults (200 mL/h/kg) [152], interpretation is difficult, because the hypoxic-ischemic insult also affects the clearance. Clearance is achieved through oxidation (CYP2C19) to an inactive metabolite, thiopentone carboxylic acid, and neonatal immature hepatic function decreases oxidizing capacity. CYP2C19 microsomal activity is approximately 30% of mature values in the third trimester of pregnancy, but increases dramatically at term [60]. Thiopentone clearance maturation is consistent with this CYP2C19 maturation. Clearance rapidly increases during the neonatal period from 33 mL/h/kg at 24 weeks PMA to 160 mL/h/kg at term; within 20% of the adult clearance [158]. Neonates (25.7–41.4 weeks PMA) undergoing surgery on the first day of life resulted in an elimination half-life of 8 h (interquartile range (IQR) 2.5–10.8) and a clearance 92 mL/min/kg (IQR 20–100) [159]. Thiopental has a low hepatic extraction ratio (0.3), exhibiting capacity limited elimination. In adults, 10–12% of thiopentone is metabolized per hour; comparable data are not available in neonates. Michaelis-Menten kinetics are reported in adults as well as in neonates. The Michaelis constant in neonates (Km 28.3 mg/L) is similar to that reported for adults (26.7 mg/L). The maximum rate of metabolism (Vmax) increases from 0.44 mg/min/kg at 24 weeks PMA to 5.26 mg/min/kg at term; an adult Vmax of 7 mg/min/kg has been reported [158].

Adverse Effects

These are similar to those described for propofol. Thiopentone has little direct effect on vascular smooth muscle tone. Cardiovascular depression is centrally mediated by inhibition of sympathetic nervous activity and direct myocardial depression through effects on trans-sarcolemmal and sarcoplasmic reticulum calcium flux [160]. There is no pain with IV injection. Because the action of thiopentone is terminated by redistribution and metabolism is slow, recovery may be very slow after an infusion of thiopentone.

Ketamine

Mechanism of Action

The analgesic properties of ketamine are mediated by multiple mechanisms at central and peripheral sites. The contribution from N-methyl-D-aspartate (NMDA) receptor antagonism and interaction with cholinergic, adrenergic, serotonergic, opioid pathways, and local anesthetic effects remain to be fully elucidated.

Pharmacodynamics

Ketamine is available as a mixture of two enantiomers; the S(+)-enantiomer has four times the potency of the R(-)-entantiomer. S(+)-ketamine has approximately twice the potency of the racemate. The metabolite norketamine has a potency that is one-third that of its parent. Plasma concentrations associated with hypnosis and amnesia during surgery are 0.8–4 μg/mL; awakening usually occurs at concentrations less than 0.5 μg/mL. Pain thresholds are increased at 0.1 μg/mL [161–163]. Data from neonates are not available.

Pharmacokinetics

Ketamine is very lipid soluble with rapid distribution. Ketamine undergoes N-demethylation to norketamine. Elimination of racemic ketamine is complicated by the R(-)-ketamine enantiomer, which inhibits the elimination of the S(+)-ketamine enantiomer [164]. Clearance in infants within the first six months of life is similar to adult rates (80 L/h/70 kg, i.e., liver blood flow), when corrected for size using allometric models [46]. In contrast, clearance in the neonate is reduced (26 L/h/70 kg) [165–167], while the Vss is increased (3.46 L/kg at birth, 1.18 L/kg at 4 years, 0.75 L/kg at adulthood [165]). This larger Vss in neonates explains, in part, why neonates require a four-fold greater dose to prevent gross motor movement than 6-year-old children do [168]. The hepatic extraction ratio is high and the relative bioavailability of oral, nasal, and rectal formulations is 30–50%.

Adverse Effects

Ketamine can cause psychotic reactions and hallucinations that can cause distress in older children. These can be ameliorated by benzodiazepines. An antisialagogue may be required to diminish copious secretions after parenteral administration. Tolerance in children may occur with repeated use. Increases in intracranial pressure can be ameliorated by maintaining normocarbia.

The use of ketamine in neonates is limited because of concerns that the NMDA antagonists cause neuronal apoptosis during periods of synaptogenesis in newborn mammals. Neonatal rats that did not undergo surgical stimulation or inflammatory response but were exposed to high-dose ketamine sustained widespread neuronal apoptosis and long-term memory deficits [169, 170]. The applicability of extrapolating rodent data to the care of human neonates continues to be debated [163, 171, 172].

Inhalation Agents

Physicochemical Properties

The chemical structures of the inhalational anesthetics are based on a polyhalogenated ether skeleton (with one exception): isoflurane and desflurane are methyl ethyl ether anesthetics and sevoflurane is a methyl isopropyl (original Table 3.1). The single exception to the ether skeleton is halothane, a polyhalogenated alkane that is infrequently used today. Desflurane differs from isoflurane only in the substitution of a fluoride atom for a chloride on the alpha carbon of isoflurane, whereas sevoflurane differs by the substitution of a trifluoromethyl group for a chloride atom on the alpha carbon of isoflurane. These minor atomic substitutions and structural differences confer substantial differences in the physicochemical and pharmacological properties of the ether anesthetics that are elucidated below (Table 3.1).

Pharmacokinetics

In the 1960s, investigators determined that the wash-in curves for halothane (Fig. 3.15), and N_2O in neonates were

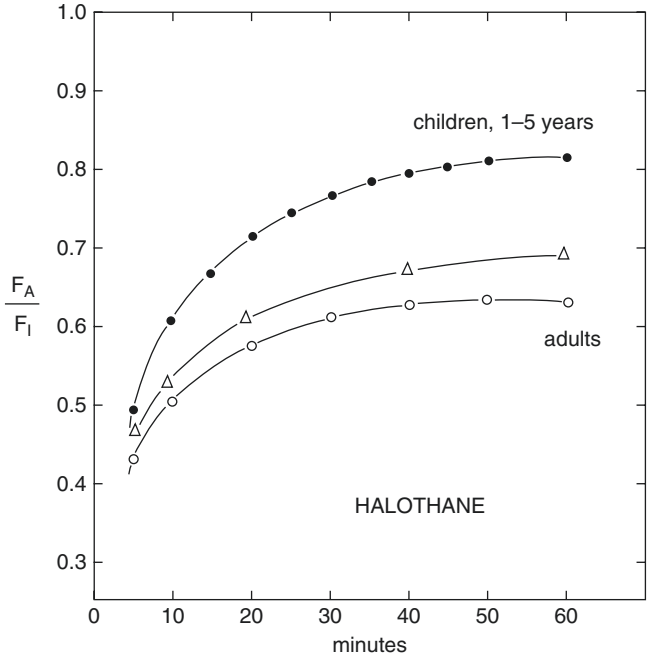
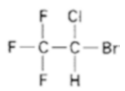
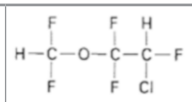
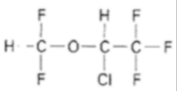
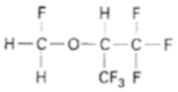
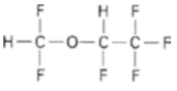


Fig. 3.15 Rate of rise of alveolar to inspired partial pressures of halothane in children and adults (reproduced with permission, Salanitre & Rackow [38]

Table 3.1 Pharmacology of inhaled anesthetics

	Halothane	Enflurane	Isoflurane	Sevoflurane	Desfluranee
Pharmacology					
Chemical structure *INSERT CHEM STRUCTURES HERE PLEASE*					
Molecular weight	197.4	184.5	184.5	200.1	168
Boiling point (°C)	50.2	56.5	48.5	58.6	23.5
Vapor pressure (mmHg)	244	172	240	157	664
Saturation concentration (%)	34	24	34	26	93
Odor	Mild, pleasant	Etheric	Etheric	Pleasant	Etheric
Solubility					
$\lambda_{b/g}$ adults	2.4	1.9	1.4	0.66	0.42
$\lambda_{b/g}$ neonates	2.14	1.78	1.19	0.66	–
$\lambda_{brain/b}$ adults	1.9	1.3	1.6	1.7	1.2
$\lambda_{brain/b}$ neonates	1.5	0.9	1.3	–	–
$\lambda_{fat/b}$ adults	51.1	–	45	48	27
MAC					
MAC_{adults}	0.75	1.7	1.2	2.05	7.0
$MAC_{neonates}$	0.87	–	1.60	3.2	9.2

b/g Blood/gas, *brain/b* Brain/blood, *fat/b* Fat/blood, *MAC* Minimum alveolar concentration (percent), λ Partition coefficient
Reproduced in part, from Ref. [39]

more rapid than in adults [38, 173]. Although the rate of increase of alveolar to inspired partial pressures of N_2O in adults is rapid, achieving an F_A/F_I ratio of 0.8 within 10 min, it is even more rapid in neonates and infants, achieving a ratio of 0.9 within 5 min. The fundamental principle underlying the pharmacokinetics of these anesthetics in neonates is the movement of inhalational anesthetics among body organs. Outside of the body, inhalational anesthetics exist in the gas phase where the concentrations and partial pressures are interchangeable (assuming the ideal gas law). However, inside the body, the concentrations of inhalational anesthetics in any fluid or solid tissue exceed the equivalent partial pressure (determined by the dissolved fraction), because they are bound to proteins and lipids. In addition, these anesthetics move across tissue membranes into the blood or from blood into tissues without impediment, following partial pressure, not concentration, gradients. This movement of anesthetics across membranes continues until the partial pressures equilibrate, despite differences in the concentrations of the anesthetics. Conceptually, this is identical to the movement of oxygen and carbon dioxide within the body. As a result, we only refer to inhalational anesthetics in terms of their partial pressures within the body.

Four factors explain the more rapid wash-in of inhalational anesthetics in neonates compared with older children and adults (Table 3.2). The first is the delivery of anesthetics to the lungs. Alveolar ventilation delivers the anesthetic and the FRC is the lung compartment into which the anesthetic is delivered [174]. The greater the ratio of the alveolar ventilation to FRC, the more rapidly the anesthetic partial pressure in the FRC increases. In neonates, this ratio is 5:1, three-fold greater than in adults, 1.5:1. The remaining factors (Table 3.2) explain the rapid wash-in of anesthetics in neonates by their effects on the uptake of anesthetics from the lungs. Although a greater cardiac output should actually slow the wash-in of anesthetic into the FRC, in neonates, it speeds the wash-in, because the greater cardiac output primarily distributes anesthetic to the vessel-rich group (VRG) of tissues (brain, heart, kidneys, and gastrointestinal and endocrine organs), which, in neonates, comprises a larger fraction (18%) of the bodyweight than it does in children/adults (6%). With the VRG receiving such a large proportion of the cardiac output, the anesthetic partial pressures in the VRG equilibrate very rapidly, leaving a large partial pressure of anesthetic in the blood returning to the heart, pressures that are similar to those in the blood that left the heart. Hence, a diminishing quantity of inhalational anesthetic is taken up from the FRC, allowing the partial pressure in the FRC to increase. At the same time, the blood and tissue solubilities of inhalational anesthetics in neonates are less than those in older children and adults. (Fig. 3.16, Table 3.1) [40, 175, 176]. This is true for the more soluble inhalational anesthetics with solubilities that are 18% less than those in neonates compared with older children and adults. However, in the cases of the less soluble anesthetics, sevoflurane and desflurane, the solubilities in neonates do not differ substantially from those in adults [40]. Hence, blood solubility differences of the less soluble inhalational anesthetics do not contribute substantively to the rapid wash-in of sevoflurane and desflurane in neonates. Similarly, age-related differences in hemoglobin, serum concentration of α_1-acid glycoprotein, and prematurity do not significantly affect the solubility of most inhalational anesthetics in blood [177]. Accordingly, the uptake of anesthetics by blood and tissues in neonates is relatively small, leaving the partial pressure in the FRC to increase unabated.

To understand the wash-in of inhalational anesthetics, the rate of rise of the anesthetic partial pressure (e.g., wash-in of anesthetic) follows an exponential curve, the variables of which are determined by the volume of the reservoir and the flow into the reservoir. The equation that describes such a wash-in is a simple, first-order exponential equation:

Table 3.2 Determinants of the rapid wash-in of inhalational agents in infants

1. Greater alveolar ventilation to functional residual capacity ratio
2. Greater fraction of the cardiac output distributed to the vessel-rich group
3. Reduced tissue/blood solubility
4. Reduced blood/gas solubility

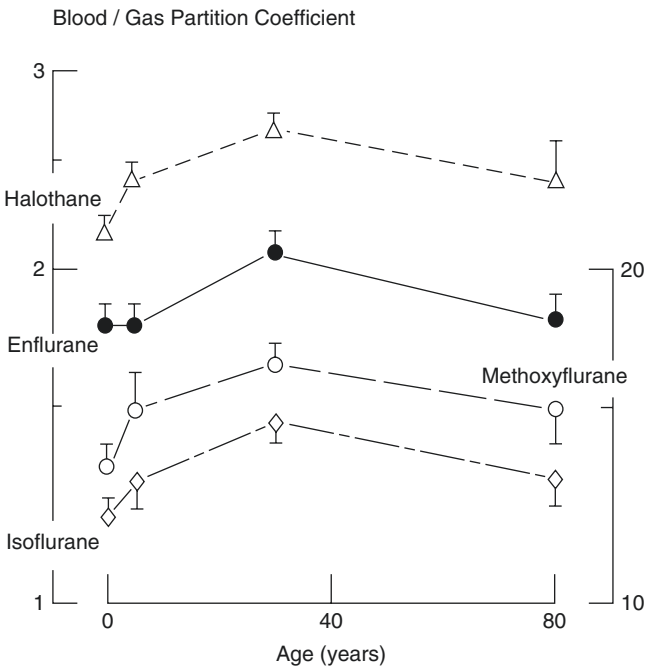


Fig. 3.16. Effect of age on the blood/gas partition coefficient of the four inhalational agents: isoflurane, enflurane, halothane, and methoxyflurane. The solubility of all four agents in neonates is 18 % less than in adults (reproduced with permission, Lerman et al. [175])

$$C / C_{o} = 1 - e^{-kt}, \text{where } k \text{ is } 1/t \tag{3.1}$$

where τ is the time constant, which is defined by Eq. (3.2):

$$\tau(\text{min}) = \frac{\text{Volume of the functional residual capacity (L)}}{\text{Alveolar ventilation (L / min)}} \tag{3.2}$$

Four time-constants are required to reach 98% equilibration of anesthetic partial pressures in the FRC. Hence, with an FRC of 0.5 L and an alveolar ventilation of 1 L/min, is 0.5 and the time to reach 98% equilibration of inspired and alveolar anesthetic partial pressure is 2 min.

The increase in anesthetic partial pressure in tissues is also determined by a simple first-order exponential curve that depends on the delivery of anesthetic to the tissues (tissue blood flow) and the capacity of the tissues for anesthetic to reach partial pressure equilibration (the product of the volume of the tissue and the solubility of anesthetic in the tissue). This is expressed by an equation that is similar to Eq. (3.2) as follows for the wash-in to the brain:

$$\tau_{\text{brain}} = \frac{\text{Volume of the brain (mL)} \times \text{Brain / blood solubility}}{\text{Brain blood flow (mL / min)}} \tag{3.3}$$

Understanding the wash-in of inhalational anesthetic into the brain is essential to appreciating the pharmacokinetics of induction of anesthesia with an inhalational anesthetic. Assuming the blood flow to the brain is 50 mL/min/100 g of brain (and the brain density is 1 g/mL) and the brain/blood solubility for a particular inhalational anesthetic in an adult is 2.0, then the time constant is as follows:

$$\tau_{\text{brain}} = \frac{100\,\text{mL} \times 2}{50\,\text{mL / min}} = 4\,\text{min} \tag{3.4}$$

Thus, the time to reach 98% equilibration of anesthetic partial pressures is 16 min. If the brain/blood solubility were halved, as in the case of a neonate [176] to 1.0, then the time to 98% equilibration would decrease by 50% to 8 min, resulting in a more rapid onset of anesthesia in the neonate and explain the early onset of cardiorespiratory sequelae.

The wash-in curves for the commonly used inhalational anesthetics have been reported for adults [178]. The alveolar to inspired concentrations for halothane reach 0.35 in the first minute of the start of anesthesia, independent of level of ventilation (Fig. 3.17). In the neonate, the wash-in of halothane in the first minute is closer to 0.5, based on the more rapid wash-in of halothane in neonates. With a maximum inspired concentration for halothane of 5% and an MAC (minimum alveolar concentration) in neonates of 0.87%, the alveolar partial pressure would be 5 × 0.5/0.87 or 2.9 × MAC. If sevoflurane were substituted for halothane, then the wash-in in the first minute would be ~0.5 for both adults and neonates (as sevoflurane is an insoluble anesthetic). With an inspired concentration of 8% and an MAC of 3.3%, the alveolar partial pressure would be 8 × 0.5/3.3 or 1.2 × MAC, which is less than one-half that with halothane. Thus, sevoflurane is less likely to cause hemodynamic depression in the neonate in the early period of anesthesia as would halothane, and a depth of anesthesia that is less than that achieved with halothane in the first minute.

The rate of increase of alveolar to inspired partial pressures of inhalational anesthetics varies inversely with the solubility in blood as follows: N_2O > desflurane > sevoflu-

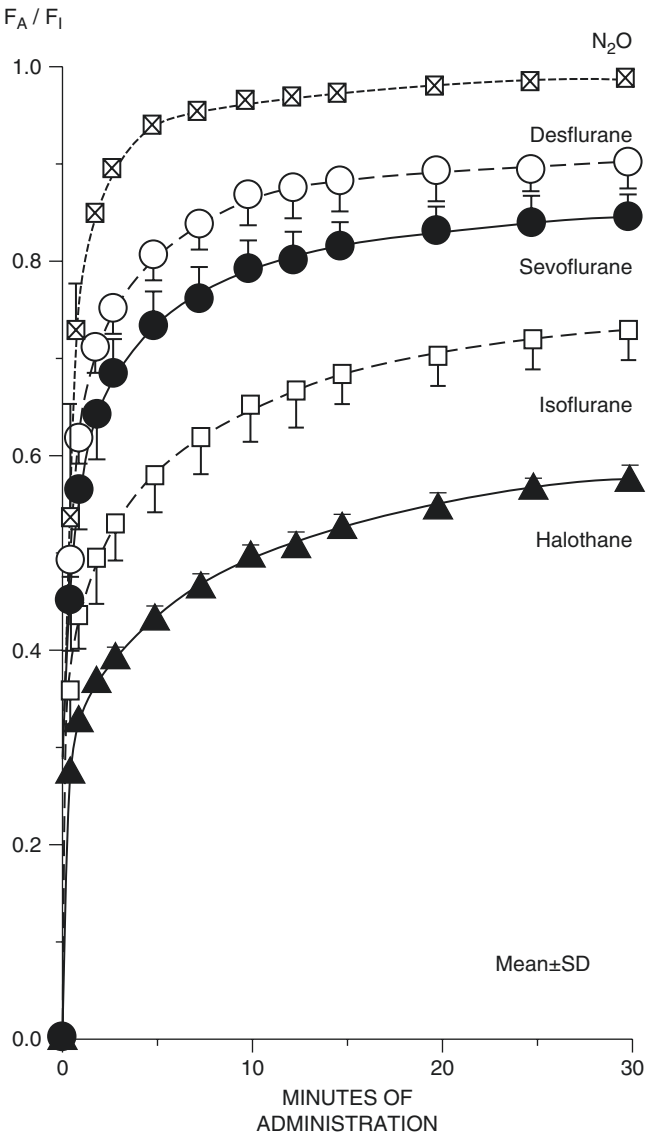


Fig. 3.17 Wash-in of N_2O, desflurane, sevoflurane, isoflurane, and halothane in adults. The order of wash-in parallels the solubility of these agents in blood (reproduced with permission from Yasuda N, et al. [178])

rane > isoflurane > enflurane > halothane > methoxyflurane (Fig. 3.17) [178]. After a step-wise change in the inspired partial pressure of less soluble anesthetics, the alveolar partial pressure equilibrates very rapidly with the new inspired partial pressure. Since the washout of these anesthetics is equally rapid (see below), the inspired partial pressure can be returned to its initial value rapidly by decreasing the inspired partial pressure. Thus, anesthetic depth can be controlled more rapidly with less soluble than with more soluble inhalational anesthetics.

The solubilities of the inhalational anesthetics in the vessel-rich tissues in neonates are approximately one-half those in adults (Fig. 3.18) [176]. These reduced tissue solubilities for halothane, isoflurane, enflurane, and methoxyflurane are attributable to two differences in the composition of tissues in neonates compared with those in adults: (1) greater water content and (2) decreased protein and lipid concentrations. The reduced tissue solubilities decrease the time for partial pressure equilibration of anesthetics in tissues (see time constant for tissues, above). Although the partial pressures of inhalational agents in tissues cannot easily be measured in vivo, they may be estimated by measuring the anesthetic partial pressure in the exhaled or alveolar gases. Thus, the reduced tissue solubilities of inhalational anesthetics in neonates speed the wash-in of anesthetic partial pressures compared with adults.

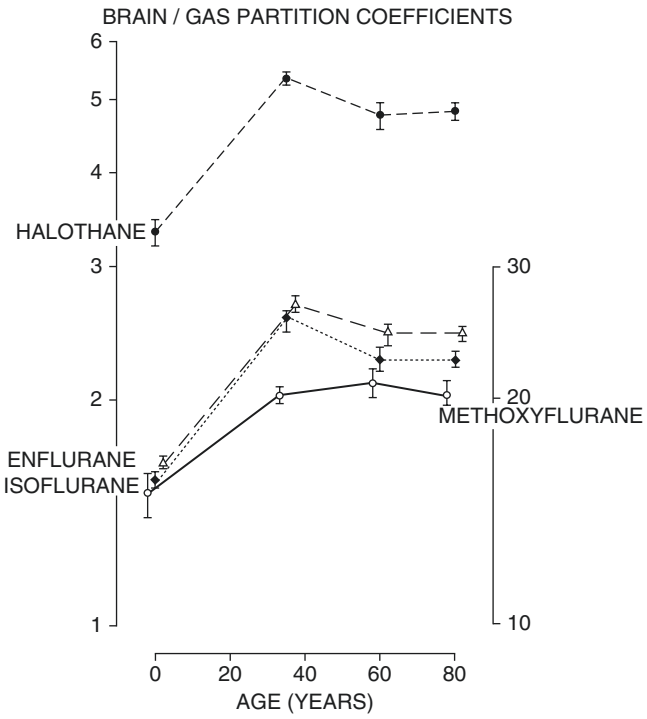


Fig. 3.18 Effect of age on the solubility of isoflurane, enflurane, halothane, and methoxyflurane in the human brain. The solubilities of all anesthetics in the neonatal brain are less than those in older adults (reproduced with permission, Lerman J, et al. [176])

The pharmacokinetics of inhalational anesthetics during the first 15–20 min depends primarily on the characteristics of the vessel-rich group, whereas the pharmacokinetics during the subsequent 20–200 min depends on the characteristics of the muscle group [174]. The solubility of inhalational anesthetics in skeletal muscle varies directly with age in a logarithmic relationship [176]. This effect of age on the solubility of anesthetics in muscle has been attributed to age-dependent increases in protein concentration in the first five decades of life and in fat content in the subsequent three decades of life [176]. Since the muscle mass in the neonate is small, this effect is attenuated.

The net effect of these differences between neonates and adults is to speed the equilibration of anesthetic partial pressures in alveoli and tissues and thereby speed the rate of equilibration of alveolar to inspired anesthetic partial pressures in neonates compared with adults [38, 173]. However, the difference in the rate of wash-in of less soluble anesthetics between neonates and adults may be less pronounced than that of more soluble anesthetics.

Ventilation

Changes in alveolar ventilation directly affect the wash-in of inhalational anesthetics: as alveolar ventilation increases, the wash-in of the anesthetics increases (Fig. 3.19) [174]. Ventilation is the primary determinant of the delivery of anesthetics to the lungs to affect the wash-in of the anesthetics. The effect of ventilation on the wash-in is more pronounced with more soluble anesthetics, for example, halothane, and less pronounced or limited with less soluble anesthetics, for example, sevoflurane, and desflurane. The reason for the differential effect of ventilation rests with the dependency of the anesthetic on its speed of delivery to achieve partial pressure equilibration: those anesthetics that are more soluble in blood (and tissues) are taken up from the lungs into blood (and tissues) more rapidly, and thus, their wash-in is slowed. The wash-in of these soluble anesthetics depends more on their delivery (alveolar ventilation) than do the less soluble anesthetics. Conversely, inhalational anesthetics such as sevoflurane and desflurane, which are less soluble in blood, are delivered to the lungs with very little of the anesthetics taken up by blood, thus facilitating a more rapid wash-in that depends less on alveolar ventilation.

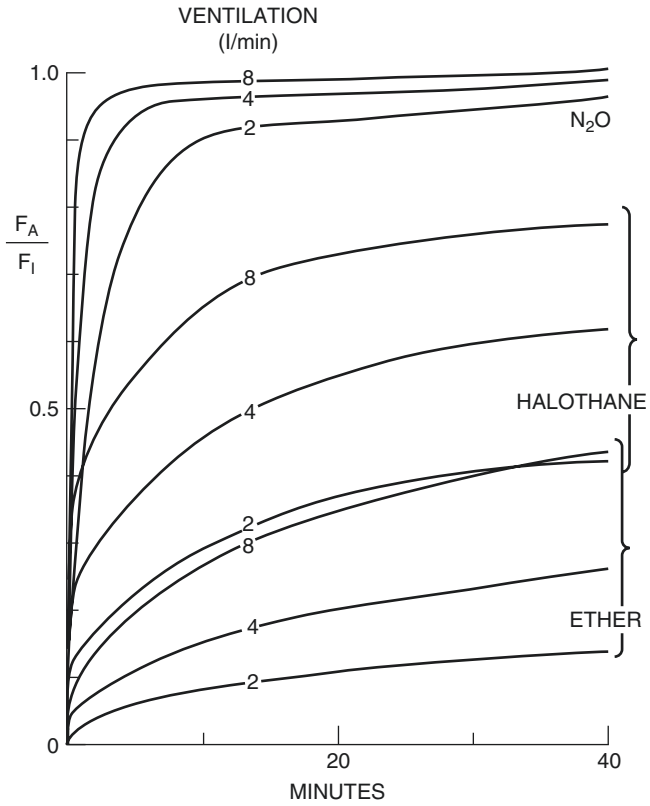


Fig. 3.19 Effect of alveolar ventilation on the wash-in of soluble (ether), intermediate (halothane), and insoluble (N_2O) anesthetics. Changes in ventilation affect the wash-in of more soluble than less soluble anesthetics (reproduced with permission, Eger EI 2nd. Anesthetic uptake and action. Baltimore: Williams & Wilkins; 1974) [174]

Cardiac Output

Changes in cardiac output inversely affect the wash-in of inhalational anesthetics as presented above: the greater the cardiac output through the lungs, the more rapidly anesthetic is removed from the lungs and the slower the wash-in of anesthetic into the alveoli [174]. In the neonate, the effect of cardiac output is paradoxical as the greater cardiac output actually speeds the wash-in, since most of the cardiac output is directed to the VRG, which comprises 18% of the cardiac output, that speeds the equilibration of alveolar to inspired anesthetic partial pressures.

Induction

Although many associate the more rapid wash-in of insoluble versus soluble anesthetics to a more rapid induction of anesthesia, this notion is probably untrue. Whereas the wash-in is determined by the pharmacokinetics of the agents, the speed of induction of anesthesia depends upon both pharmacokinetic and pharmacodynamic factors including (1) the rate of equilibration of anesthetic partial pressures (determined by the four factors in Table 3.2), (2) the maximum inspired concentration, (3) airway irritability, and (4) the MAC value. It is the interaction of these four factors that determines the relative speed of induction of anesthesia.

The rate of wash-in of inhalational anesthetic into the lungs varies inversely with the solubility of inhalational anesthetics in blood as outlined above [178]. However, only sevoflurane and halothane are devoid of irritating the upper airway when delivered by face mask. Although less soluble anesthetics wash-in to the FRC more rapidly than more soluble anesthetics, the more rapid wash-in may be offset by the limited maximum concentration deliverable from the vaporizer (overpressure technique) and their greater MAC as described on p.30 (Table 3.1).

Control of Anesthetic Depth

Two feedback mechanisms modulate the depth of anesthesia during inhalational anesthesia: respiratory and cardiovascular. During spontaneous ventilation, respiratory depression limits the depth of anesthesia by stopping the delivery of anesthetic to the lungs. As the depth of anesthesia increases, alveolar ventilation decreases, the neonate arouses from anesthesia as the anesthetics are redistributed away from the VRG and spontaneous ventilation resumes. This is known as a ***negative feedback*** effect [179]. This protective mechanism permits the use of inspired concentrations of inhalational anesthetics several-fold greater than MAC (overpressure technique) while protecting against excessive circulatory depression. However, if ventilation is controlled, this protective mechanism is bypassed. The alveolar to inspired anesthetic partial pressure ratio increases relentlessly as cardiac output decreases. This decrease in cardiac output limits the removal of anesthetic from the lung, leading to a further increase in the alveolar partial pressure of anesthetic. This is known as a ***positive feedback*** effect [179]. In such a circumstance, this leads to a downward spiral that might profoundly depress the cardiovascular system resulting in death if the cycle is not interrupted [179].

These feedback loops hold particular relevance for neonates. When halothane was administered to neonates, hypotension (and bradycardia) occurred frequently; however, when sevoflurane was introduced, despite the more rapid wash-in of this new insoluble anesthetic, circulatory instability did not occur. As described on P.30 [THIS MANUSCRIPT], the slower wash-in but greater achievable MAC-multiple of halothane offsets the more rapid wash-in of sevoflurane with the smaller achievable MAC-multiple of sevoflurane, introducing an element of safety with the later agent.

Shunts

Shunts exist in two forms: left-to-right or right-to-left. Left-to-right shunts refer to conditions in which blood recirculates through the lungs (usually an intracardiac defect such as a ventricular septal defect). In contrast, right-to-left shunts refer to conditions in which venous blood returning to the heart bypasses the lungs (as in an intracardiac (cyanotic heart defect) or intrapulmonary (pneumonia or an endobronchial intubation) defect. In general, left-to-right shunts do not significantly affect the pharmacokinetics of potent inhalational agents, provided cardiac output remains unchanged. In contrast, right-to-left shunts can significantly delay the wash-in of inhalational anesthetics [180]. The magnitude of the delay with a right-to-left shunt depends on the solubility of the anesthetic: the less soluble the anesthetic (N_2O, desflurane, and sevoflurane), the more delayed the wash-in compared with that of the more soluble anesthetics. These effects are independent of the anatomical level of right-to-left shunts: intracardiac or intrapulmonary (as in the case of an endobronchial intubation).

To understand why right-to-left shunts affect the pharmacokinetics of inhalational anesthetics and less soluble anesthetics, in particular, it is useful to consider a simplified model of the lung in which each lung is represented by one alveolus and each lung is perfused by one pulmonary artery (Fig. 3.20) [39]. When the tracheal tube is positioned with its tip at the midtrachea level (Fig. 3.20a), ventilation is divided equally between both lungs, thereby yielding equal anesthetic partial pressures in both pulmonary veins (PV = 1). However, when the tip of the tube is advanced into the right bronchus (Fig. 3.20b), all of the ventilation is delivered to one lung, that is, the ventilation to that lung is doubled and ventilation to the nonventilated lung is zero. Under these conditions, the partial pressure of CO_2 remains unchanged. When a soluble anesthetic is administered in the presence of an endobronchial intubation (right-to-left shunt), the partial pressure of anesthetic in the combined pulmonary veins is approximately the same as in the presence of a tracheal intubation. The similar anesthetic partial pressure occurs because the increased ventilation to the ventilated lung compensates to a large extent for the shunt and speeds the increase in alveolar to inspired anesthetic partial pressures. However, when a less soluble anesthetic is administered in the presence of a right-to-left shunt, the effects on the wash-in of the inhalational agent are quite dramatic. In this case, the increase in ventilation to the ventilated lung minimally increases the wash-in of the anesthetic (Fig. 3.20c). As a consequence, the minimal increase in wash-in to the ventilated lung cannot offset the effects of the shunt. The anesthetic partial pressure in the combined pulmonary vein thus lags behind the partial pressure in the veins when both lungs

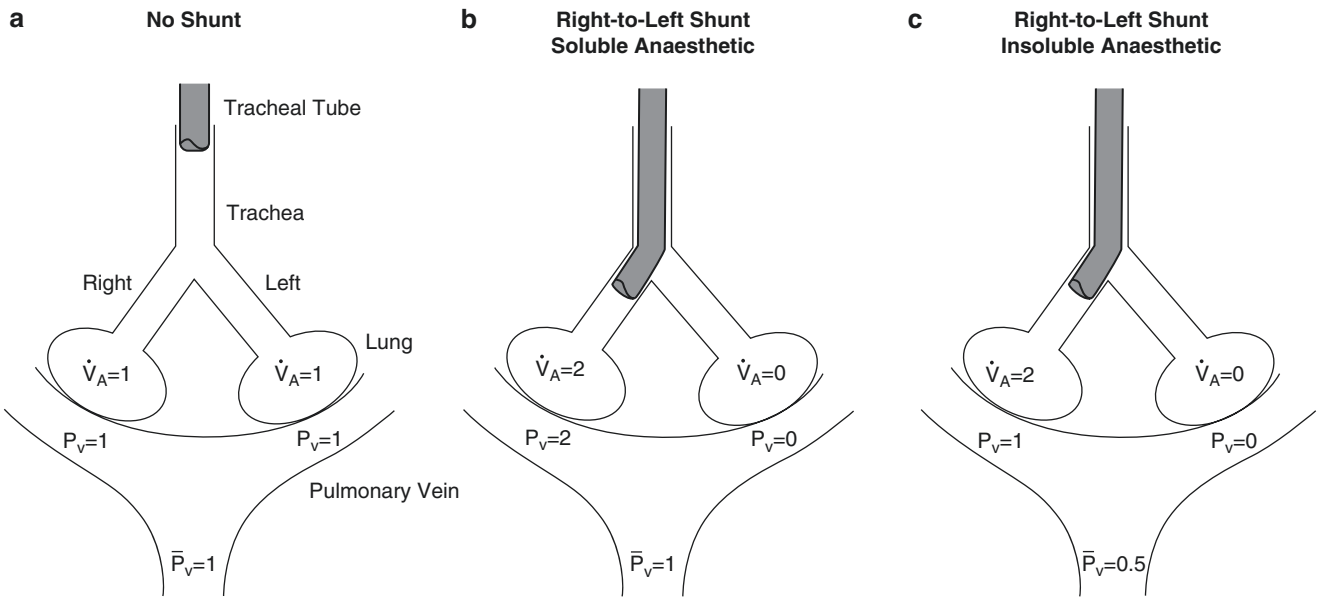


Fig. 3.20 Effect of shunt on the wash-in of anesthetic partial pressure in blood. (**a**) illustrates the normal wash-in with no shunt, equal ventilation to both lungs and normocapnia. (**b**) illustrates the effect of a right-to-left shunt (via an endobronchial intubation) on the wash-in of a soluble anesthetic. Normocapnia is maintained, and hypoxic pulmonary vasoconstriction is negligible. The doubled ventilation to the intubated lung offsets the effect of the shunt. The wash-in is similar to (**a**). However, (**c**) illustrates the dramatic effect of a right-to-left shunt on the wash-in with a less soluble anesthetic. Since the increased alveolar ventilation to the intubated lung does not substantively affect the wash-in to the lung, when the blood from the ventilated lung combines with that from the shunted lung, the net effect is a slower wash-in of anesthetic (with permission, Lerman J [39].)

were ventilated. Induction of anesthesia with a less soluble anesthetic is thereby slower in the presence of a right-to-left shunt than in the absence of a shunt. The less soluble anesthetics, desflurane and sevoflurane, are two such anesthetics whose wash-in characteristics may be significantly slowed in the presence of a right-to-left shunt. These anesthetics would require supplemental IV medication to maintain a steady and deep level of anesthesia.

The wash-in of halothane has been evaluated in children with fenestrated Fontans before and after closure of the fenestration [180]. The authors noted that before the fenestration was closed (the right-to-left shunt was open), the wash-in of halothane as determined by the increase in arterial to inspired partial pressures was delayed compared with that after the fenestration was closed. Closure of the fenestration increased the pulmonary to systemic blood flow ratio from 0.58 to 0.88. Importantly, they noted that the increase in the end-tidal partial pressure of halothane did not parallel the arterial partial pressure. This observation is consistent with published evidence that the correlation between the end-tidal and arterial partial pressures of a gas (carbon dioxide) in children with cyanotic heart disease is poor [181].

Metabolism

The metabolism of inhalational anesthetics is discussed below under Renal and Hepatic effects.

Emergence

The washout of inhalational agents follows an exponential decay (the inverse of the wash-in curve) [178]. The order of the washout of the anesthetics parallels their blood/gas solubilities; that is, the anesthetic that is washed out first, desflurane, is the least soluble in blood [178]. The order of washout in children is expected to be similar to that in adults.

Recovery of motor function in rats parallels the washout of inhalational anesthetics from fastest to slowest: desflurane < sevoflurane < isoflurane < halothane [182]. Notably, the rate of recovery increases in parallel with the duration of anesthesia [178]. In studies in which the recovery from two or more inhalational agents were compared, the end-tidal concentrations of the anesthetics were maintained at approximately 1 MAC until the conclusion of surgery after which the anesthetics were abruptly discontinued [183–185]. In this paradigm, it is not surprising to find that the rates of recovery paralleled the rates of washout, which in turn paralleled the blood solubilities of the inhalational agents. In clinical practice however, anesthetic concentrations are gradually tapered as the end of surgery approaches. This practice attenuates the differences in the rates of recovery amongst inhalational agents.

In neonates, recovery after inhalational anesthesia is somewhat slower than that predicted solely by the washout curves. In part, this area of investigation has been hampered by a lack of consensus on the essential factors associated with emergence in the neonate [186]. Many anesthesiologists have struggled to explain why neonates recover at a slower rate than expected after a brief anesthetic with only inhalational anesthesia. Nonetheless, infants recover more rapidly after desflurane than with sevoflurane and halothane [187]. No clear answers to explain this curiosity have been forthcoming.

Pharmacodynamics

In 1969, the MAC of halothane was noted to increase as age decreased [188]. The MAC of halothane reached its maximum value (1.1%) in the youngest age group, which included 2 neonates and 4 infants 1–6 months of age. Based on this MAC measurement, one study cautioned against the use of halothane in neonates because it caused more hypotension than it did in older infants [189]. Clinicians deduced at the time that neonates were more sensitive to the myocardial depressant effects of halothane than children. Subsequently, when we measured the MAC of halothane in neonates as a group distinct from older infants 1–6 months of age, the MAC in the former group, 0.87 ± 0.1%, was 15–25% less than that in the latter, 1.2% [99]. Furthermore, when 1 MAC of inhalational anesthetics were administered, the systolic blood pressure and heart rate responses in neonates were similar to those in older infants [99, 190, 191]. The MAC (mean ± SD) values in full-term neonates for the inhalational anesthetics in use today are: 1.60 ± 0.01% for isoflurane [192], 9.2 ± 0.02 % for desflurane [190] and 3.3 ± 0.2% for sevoflurane [191]. Also, there is evidence that the primary cause of the increased sensitivity of neonates to cardiodepression by inhalational anesthetics may be attributed to the immaturity of the cardiovascular system [193]. Using echocardiography, the cardiodepressant effects of halothane and isoflurane in concentrations up to 1.5 MAC in neonates were noted to be greater than in older infants [194]. The increased susceptibility of neonates to the depressant effects of inhalational anesthetics has been attributed, in part, to a decrease in myocardial contractile elements, the decrease in calcium sensitivity of myocardial fibers [193], and the incomplete sympathetic innervation of the heart and vascular system. Evidence also indicates that both pressor and depressor baroresponses are depressed in the presence of isoflurane in the preterm and full-term neonate [195]. These data suggest that the magnitude of the cardiovascular depression by inhalational anesthetics at 1 MAC in neonates is similar to that reported in older infants and that at concentrations greater than 1 MAC, it may be greater than in older infants.

To attenuate the cardiodepressant effects of inhalational anesthetics in neonates, the heart rate should be maintained

and preload optimized. Neonatal myocardium evolves during the first month after birth, improving in ventricular compliance [196]. Because neonates depend on a rapid heart rate to maintain cardiac output, cardiovascular depression particularly in the presence of halothane, can be reversed or offset in part by intravenous atropine (0.02 mg/kg) [194, 197]. To optimize preload, balanced salt solution or albumen in a volume of 5–20 mL/kg, should be administered before anesthesia is induced [98]. Neonates who have had cardiorespiratory dysfunction in the presurgical period or were managed in the Neonatal Intensive care unit, often present to the operating room relatively dehydrated because of aggressive diuretic therapy and/or third space fluid losses. After rehydration but in the absence of chronotropic agents, systolic arterial pressure decreases ≈20–25% at 1 MAC halothane, desflurane and sevoflurane compared with awake values in neonates, with either no changes or minimal decreases in heart rate [99, 190, 191]. Similar responses have been reported with 1 MAC of these anesthetics in infants 1–6 months of age.

Curiously, the MAC values for sevoflurane in neonates and infants 1–6 months of age are similar, 3.3 and 3.2%, respectively [191]. It remains unclear why the relationship between the MAC of sevoflurane and age in infancy differs from that for the other inhalational anesthetics. Whether the conformational structure of sevoflurane, a methyl isopropyl ether, or some other physicochemical characteristic is responsible for this unique relationship between MAC of sevoflurane and age remains unclear.

The MAC of isoflurane decreases steadily in neonates as gestational age decreases to 24 weeks (Fig. 3.14) [98]. Not only did this study characterize the relationship between the MAC for isoflurane in preterm neonates and age, but it also confirmed the notion that neonates as young as 24 weeks gestation respond to noxious stimuli predictably. Although several explanations have been posited to explain the age-dependent change in MAC in the perinatal period including residual effects of placentally transmitted female hormones, central nervous system substance P, and maturation of the central nervous system, the cause remains speculative.

Several factors moderate the MAC of inhalational anesthetics in infants and children. The MAC of halothane in children with cerebral palsy and severe mental retardation is approximately 25% less than that in children without disabilities [198]. Whether these same relationships are true in neonates has not been established. Acute administration of barbiturates and benzodiazepines decreases MAC [199, 200], chronic administration of similar medications (such as in the case of children who have been treated with anticonvulsants) does not affect MAC [201]. The effects of specific anticonvulsants such as valproic acid and phenytoin on the MAC of inhalational agents remains unclear. Adults who are homozygote for melanocortin for desflurane require ~20% more anesthetic (6.2% vs 5.2%) than for brunettes [202].

The additivity of MAC fractions of inhalational agents (as well as N_2O) is well established. However, the concept of additivity in children 1–3 years of age does not hold for all inhalational agents: the additive contribution holds for the MAC of halothane and isoflurane [203, 204] but not for the MAC of sevoflurane and desflurane [191, 205]. Sixty percent N_2O decreases the MAC of sevoflurane in young children by only 24% and that of desflurane 22% [191, 205]. Whether the same holds in neonates is unknown. Additional evidence from the MAC response to tracheal intubation supports this attenuated effect of N_2O on the MAC of sevoflurane in children [206]. This differential effect of nitrous oxide on the MAC values of inhalational agents in children and of its effect on the MAC of sevoflurane and desflurane between children and adults has not been explained.

Although N_2O is a common adjunct to general anesthesia, it is infrequently used in neonates because their surgery is often emergent and includes the risk of bowel distention and there is a risk of adverse effects from high oxygen concentrations. The avoidance of N_2O in patients who have bowel obstruction or gas-filled closed spaces is well accepted [207]. However, its avoidance in neonates who are at risk for oxygen toxicity is less clear. The maximum PaO_2 currently recommended to preclude oxygen toxicity is 80 mmHg (that is, a SaO_2 of 93%). This value lies at the shoulder of the steep descending portion of the oxyhemoglobin dissociation curve. If N_2O were used to maintain the arterial oxygen tension below this value, then any minor difficulty with the airway could lead to a rapid oxygen desaturation. This potential problem would be mitigated if nitrogen supplanted N_2O since the former is 34 times less soluble in blood than the latter. As a result, most recommend N_2O be avoided and replaced with an air/oxygen mixture in neonatal surgery.

The MAC responses to stimuli other than skin incision; ie., tracheal intubation, LMA insertion, extubation, and return of wakefulness (MAC awake) have also been determined in children, although their applicability to neonates has not been established [208].

Central Nervous System

For the past decade, the anesthesia literature has been dominated and preoccupied with the effects of anesthesia on neuroapoptosis in the brain of the human neonate. Neuroapoptosis is discussed further in Chapter 18 (Do anesthetic drug harm neonates? A global perspective) and will not be discussed further here.

Although cerebral blood flow (CBF) is autoregulated, there are limits in mean blood pressures beyond which CBF is pressure passive. Evidence suggests that neurological sequelae are increasingly likely when the CBF decreases below 20 mL/kg/min. However, there is a dearth of evidence to support this notion in neonates and during general anesthesia [209]. CBF to the cortex is 3–4-fold greater than to

white matter, in part, explaining the increasing vulnerability to periventricular leukomalacia in the perinatal period.

In general, all potent inhalational agents depress the central nervous system with dose-dependent decreases in the cerebral vascular resistance and the cerebral metabolic rate for oxygen. The decrease in vascular resistance causes a reciprocal increase in CBF that starts at 0.6 MAC [210]. The extent of the increase in CBF however, depends on the inhalational agent: halothane > enflurane > isoflurane [210]. The effects of sevoflurane on CBF are similar to those of isoflurane, however the effects of desflurane differ substantively. Desflurane blunts the cerebral autoregulatory response [211, 212]. The net effect of inhalational agents is to increase the ratio of the cerebral blood flow to metabolic rate, with desflurane increasing the ratio the greatest and therefore is the least preferred agent in these children.

The effects of inhalational agents on the cerebral blood flow in infants and children are poorly understood. Preliminary data suggest that cerebral blood flow velocity in children varies directly with the end-tidal carbon dioxide partial pressure during halothane anesthesia [213]. Cerebral blood flow velocity increases as the concentration of halothane increases [214] but does not change significantly in the presence of increasing concentrations of isoflurane. In a retrospective study of infants <6 months of age who were anesthetized with 1 MAC sevoflurane and were normocapneic, a MAP >35 mmHg maintained positive regional cerebral oxygen saturations, that is the oxygen delivery exceeded the cerebral metabolic rate of oxygen consumption [215].

The EEG activities of desflurane and sevoflurane are similar to those of isoflurane [216, 217] although the activity of sevoflurane differs substantially from that of halothane [218]. The shift of power of the EEG from low (1–4 Hz) to medium frequencies (8–30 Hz) is greater for halothane than it is for sevoflurane. The unique EEG tracing in the neonate evolves rapidly through gestation and with postnatal age in infancy [219–221]. During the neonatal period, up to 2% sevoflurane exerts limited effects on the EEG; however, by 3–5 months postnatal age, the EEG is responsive to increasing sevoflurane concentrations. The clinical relevance of these EEG differences remains unclear at this time, although the BIS responses to sevoflurane, which are derived from the EEG, differ substantively from those of halothane [222, 223]. Since brain monitors are infrequently used in neonates, this issue is moot.

In children who were anesthetized with sevoflurane, both epileptiform activity in the form of myoclonic movement of the extremities and transient spike and wave complexes on EEG have been reported in a very small number of young children [224–227]. To determine whether these involuntary movements could have as their origin a cortical focus, the EEG was analyzed for evidence of seizure activity in children who had been anesthetized with either halothane or sevoflurane [221]. None of the children displayed either clinical or EEG evidence of seizure activity. The EEG patterns for both halothane and sevoflurane were characteristic even though all of the children had been premedicated with midazolam**.** The association between myoclonic movement and seizures during sevoflurane anesthesia remains tenuous [228]. In neonates, only a single case of a seizure has been reported after sevoflurane anesthesia [229]. EEG differs substantively through gestation [220]. A meta-analysis of studies in which amplitude-integrated EEG and/or NIRS were monitored during anesthesia was unable to identify clear monitoring strategies for EEG and NIRS in neonates [230]. However, 3–5% of children experience at least 1 seizure in childhood, with the greatest incidence occurring in infants <1 year of age [231, 232]. Since epileptiform activities are weakly associated with clinical seizures [233], the clinical relevance of this activity in the perianesthetic period is unknown.

Cardiovascular System

Inhalational agents affect the cardiovascular system either directly (by depressing myocardial contractility or the conduction system, or by dilating the peripheral vasculature) or indirectly (by affecting the balance of parasympathetic and sympathetic nervous systems, neurohumoral, renal or reflex responses). The cardiovascular responses to inhalational agents in children are further complicated by maturational changes in the cardiovascular system and its responsiveness to these anesthetics [193, 196]. This is particularly a concern in neonates, although few studies have specifically addressed myocardial contractility in the neonate.

Assessment of cardiovascular variables in infants and children presents a challenge for clinicians. Blood pressure may be measured either invasively (arterial line) or noninvasively. Electrocardiography is routinely used in all age groups to detect arrhythmias. In contrast to blood pressure and electrocardiography, measurement of cardiac output and myocardial contractility are much more difficult to quantitate in this age group. Two-dimensional echocardiography and impedance cardiometry have been used to estimate cardiac output and myocardial contractility in infants and children [194, 234–236], although the echocardiographic measurements are subject to variability depending on the preload and afterload. Load-independent derived echocardiographic variables (stress-velocity and stress-shortening indices) have since improved the accuracy of echocardiographic estimates of myocardial function and are used with increasing frequency [237].

In neonates, several factors affect the blood pressure responses to inhalational agents including the particular inhalational anesthetic, the dose, the preload status of the infant, the presence of co-existing diseases, and the techniques used to measure the systemic pressure (invasive versus noninvasive) and cardiac function (echocardiography). Most stud-

ies demonstrated modest, dose-dependent decreases in blood pressure with all of the inhalational agents. At ~1 MAC, systolic blood pressure decreased ~24% with halothane, 30% with sevoflurane, and 34% with desflurane [99, 190, 191]. Systolic pressures may further decrease with concentrations up to 1.5 MAC. Few data exist regarding the hemodynamic responses beyond 1.5 MAC. On balance, all of the inhalational agents (in concentrations up to 1.5 MAC) modestly depress systemic blood pressure in parallel with the dose.

Many neonates arrive in the operating room from the NICU relatively hypovolemic. To restore euvolemia and attenuate the decrease in blood pressure under anesthesia, we administer at least 10 mL/kg IV balanced salt solution before anesthesia is induced [98]. Defining hypotension in neonates and infants (<6 months of age) is controversial. Two definitions are currently recognized for hypotension under anesthesia in this age group: a decrease in systolic or mean arterial pressure >20% below the awake or baseline value (relative hypotension), or an absolute value such as a mean arterial pressure <35 mmHg or a systolic pressure of ≤45–50 mmHg [238–241]. The frequency of hypotension, both relative and absolute, during anesthesia is greatest before surgical incision, in emergency procedures and with decreasing age (e.g., in preterm infants) [240, 242]. The feared complication of persistent hypotension in the preterm and full-term neonate is neurocognitive dysfunction. Decreases in blood pressure and prematurity predispose to cerebral oxygen desaturation under anesthesia, with almost 20% of neonates experiencing cerebral desaturation >20% from baseline. However, recent evidence suggests that <20% decreases in systolic blood pressure in neonates predicted <10% probability of cerebral desaturation occurring, although a decrease in systolic blood pressure >37.5% predicted >90% probability of cerebral desaturation [243]. Severe hypotension (<25 mmHg), which is associated with cerebral oxygen saturation (<70%), occurs rarely (in ~2% of infants) under anesthesia [244]. Currently, we posit that hypotension under anesthesia is an unlikely precursor for neurocognitive dysfunction.

The effects of inhalational anesthetics on myocardial contractility and cardiac output in the neonate are incompletely understood. Cardiac output in neonates decreases at 1.0 and 1.5 MAC halothane and isoflurane similarly [194]. Knowing the limited effects of sevoflurane and desflurane on myocardial contractility, one might expect that these anesthetics decrease cardiac output and myocardial contractility at 1 and 1.5 MAC less than halothane [245]. To offset the circulatory depression by inhaled agents, intravenous atropine and a bolus of balanced salt solution (10 mL/kg) before induction of anesthesia may be effective in neonates [197, 246, 247].

The mechanism by which inhalational agents depress myocardial function remains controversial. Studies in both animal and human myocardial cells suggest that the potent inhalational agents, halothane, isoflurane, and sevoflurane, directly depress myocardial contractility by decreasing intracellular Ca^{2+} flux. Inhalational agents decrease the Ca^{2+} flux by their action on the calcium channels themselves, ion exchange pumps, and the sarcoplasmic reticulum [193]. Inhalational agents may also attenuate contractility of ventricular myocytes via voltage-dependent L-type calcium channels (which are responsible for the release of large amounts of calcium from the sarcoplasmic reticulum) [193, 196, 248, 249].

That neonates and infants are more sensitive to the depressant actions of inhalational agents than older children is supported by experimental evidence of maturational differences between neonatal and adult rat, rabbit, and feline myocardium [249–251]. Structural differences that may account, in part, for the changes in myocardial sensitivity to inhalational agents with age include a reduction in contractile elements, immature sarcoplasmic reticulum, and functional differences in calcium sensitivity of the contractile elements, calcium channels, and the sodium-calcium pump in the neonatal myocardium [193, 248–254]. The determinants of Ca^{2+} homeostasis in ventricular myocardial cells in the neonate depend on trans-sarcolemma Ca^{2+} flux to a far greater extent than on the sarcoplasmic reticulum [193]. This is based upon a growing body of experimental evidence that includes the finding that the concentration of the Na^{+}-Ca^{2+} exchange protein in the neonatal myocardium, a protein that regulates trans-sarcolemma flux of Ca^{2+}, exceeds that in adult cells by 2.5 fold and that its concentration decreases with age as the concentration of L-type voltage-dependent calcium channel increases [250]. Furthermore, halothane reversibly inhibits the Na^{+}-Ca^{2+} exchange protein in immature myocardial cells [250]. The sarcoplasmic reticulum is poorly developed in neonatal myocardial cells and this finding weighs heavily against the SR being the major source of Ca^{2+} required for myocardial contractility.

The baroreflex response is also depressed in neonates with both halothane [255] and isoflurane [195], albeit to a greater extent with the former than the latter. Given the greater incidence of hypotension in neonates and infants than in older children, an intact baroreflex could offset, in part, the cardiovascular consequences. However, inhalational agents blunt this response, leaving the infant vulnerable to the cardiovascular depressant actions of inhalational agents. Prophylactic anticholinergics and preload augmentation may attenuate the decrease in cardiac output in the presence of inhaled anesthetics.

Inhalational anesthetics vary in their effect on cardiac rhythm. Halothane may slow the heart rate, in some cases, leading to junctional rhythms, bradycardia, and asystole. These are dose-dependent responses. Three mechanisms have been proposed to explain the genesis of halothane-associated dysrhythmias: a direct effect on the sinoatrial node, a vagal effect, or an imbalance in the parasympathetic/sympathetic

tone. It has also been suggested that the etiology of the bradycardia during halothane anesthesia may be a withdrawal of sympathetic tone. Bradycardia is particularly marked in the neonate, presumably because parasympathetic influences predominate over the sparse sympathetic innervation of the myocardium in this age group. Junctional rhythms are also common during halothane anesthesia. Atrial or ventricular ectopic beats are rare except in the presence of hyper- or hypocapnia. In infants anesthetized with halothane, 10 μg/kg atropine increases the heart rate ≥50% and promotes sinus rhythm [256]. This dose of atropine also increases blood pressure in infants ≥6 months of age and children.

Halothane also sensitizes the myocardium to catecholamines, particularly during hypercapnia. It decreases the threshold for ventricular extrasystoles during epinephrine administration three-fold [257–259]. In contrast, isoflurane, desflurane, and sevoflurane maintain or increase heart rate during the early induction period of anesthesia [190, 191, 234, 236, 245, 246, 260–263]. When bradycardia occurs in an anesthetized neonate, the primary cause is always hypoxia, even during anesthesia before other causes such as a direct drug effect are given serious consideration. The ether anesthetics, isoflurane, desflurane, and sevoflurane, do not sensitize the myocardium to catecholamines to the same extent as halothane [257, 258, 264]. The mechanism by which the sinus node controls automaticity is incompletely understood but may include K currents, hyperpolarization-activated current, and T and L forms of Ca^{2+} currents [193]. Moreover, developmental changes in these channels likely account, in part, for the differential effects of inhalational agents on heart rate with age [252].

Respiratory System

Inhalational agents significantly affect respiration in infants in a dose-dependent fashion via effects on the respiratory center, chest wall muscles, and reflex responses. Halothane depresses respiration by decreasing tidal volume and attenuating the response to carbon dioxide [265–267]. This depression is offset in part, by an increase in the respiratory rate [266, 267]. These ventilatory responses to halothane are age-dependent; minute ventilation in infants decreases to a greater extent than in children [268]. In infants and young children, intercostal muscle activity is inhibited at greater concentrations than the diaphragm [265, 269]. This effect is most pronounced in preterm and full-term neonates and infants and when a tracheal tube is used in place of an LMA [270]. Isoflurane, enflurane, sevoflurane, and desflurane depress the ventilatory drive and tidal volume and attenuate the respiratory responses to carbon dioxide [265, 267, 271–277]. The increase in respiratory frequency that follows respiratory depression may not restore minute ventilation to preanesthetic levels.

Sevoflurane depresses respiration to a similar extent as halothane up to 1.4 MAC but depresses respiration to a greater extent than halothane at concentrations >1.4 MAC in adults [271]. Sevoflurane does not decrease the tone of the intercostal muscles to the same extent as halothane [269, 273]. The compensatory changes in respiratory rate differ among the anesthetics; respiratory rate increases at ≥1.4 MAC halothane, is unchanged with isoflurane but decreases at ≥1.4 MAC enflurane [266, 267]. When 8% sevoflurane was compared with 5% halothane, minute ventilation and tidal volume decreased, and respiratory rate increased with both agents to similar extents [278].

Renal

The potent inhalational agents may affect renal function via four possible mechanisms: cardiovascular, autonomic, neuroendocrine, and metabolic. Although the first three mechanisms pose no direct threat to renal function, the fourth mechanism, metabolism, is a serious clinical concern that has resulted in renal dysfunction and death after some inhalational anesthetics.

Inhalational agents are metabolized in vivo to varying extents (Table 3.3). Halothane is the inhalational anesthetic that is most metabolized in vivo but releases very little fluoride in the inorganic form. Most of the fluoride that is liberated from the metabolism of halothane exists in an organic form, trifluoroacetate. This compound has been linked to halothane hepatitis (see below). Metabolism of inhalational agents by the CYP450 2E21 releases inorganic fluoride [279]. Sevoflurane releases the most fluoride of the available anesthetics, followed by isoflurane and desflurane, proportional to the extent of metabolism (Table 3.3). Even after prolonged anesthesia, 131 MAC•h isoflurane, the cumulative inorganic fluoride concentration is small [280]. The metabolism of sevoflurane yields both an inorganic and organic fluoride moiety [281]. The organic form, hexafluoroisopropanol (HFIP), is rapidly conjugated and excreted by the kidneys [281]. It poses minimal threat to renal function in humans; however, inorganic fluoride that is released from these three ether anesthetics has garnered great interest in establishing a relationship between inhalational anesthetics and renal dysfunction.

Peak plasma concentrations of inorganic fluoride after exposure to inhalational agents follow an order that is similar

Table 3.3 In vivo metabolism of inhalational agents

Inhalational agent	% Metabolized
Methoxyflurane	50%
Halothane	20%
Sevoflurane	5%
Enflurane	2.4%
Isoflurane	0.2%
Desflurane	0.02%

to that **in** Table 3.3): methoxyflurane > sevoflurane > enflurane > isoflurane > halothane ≈ desflurane [282–286]. In the case of methoxyflurane, two metabolites are produced: inorganic fluoride and oxalic acid. Both have been implicated in the pathogenesis of renal dysfunction although clinically, the renal injury was more consistent with the concentration of inorganic fluoride rather than oxalic acid [287]. Subsequent studies demonstrated that >2.5 MAC•h methoxyflurane resulted in subclinical nephrotoxicity erroneously attributed to a plasma concentration of inorganic fluoride that exceeded 50 μM and that >5 MAC•h resulted in frank nephrotoxicity also erroneously attributed to concentrations that exceeded 90 μM [288]. These clinical concerns led to the voluntary withdrawal of methoxyflurane from clinical practice.

In contrast to the adult experience with methoxyflurane, renal dysfunction was not a feature after this anesthetic in children. The peak plasma concentrations of inorganic fluoride in children anesthetized with methoxyflurane were significantly less than that in adults after an equivalent anesthetic exposure [289]. The reduced plasma concentrations of fluoride in children were attributed to several possible factors including a decreased metabolism of methoxyflurane, greater uptake of fluoride by bone, increased excretion of fluoride ions, or a reduced renal sensitivity to fluoride in children. Another plausible explanation for the reduced plasma concentrations of inorganic fluoride in children may have been an immature CYP450 2E1 isozyme system in the kidneys (see below).

That the plasma concentrations of inorganic fluoride in children who were anesthetized with sevoflurane were similar to or greater than those after enflurane raised concerns about possible renal dysfunction after prolonged exposure to sevoflurane [290–292]. However, despite large plasma concentrations of inorganic fluoride after sevoflurane anesthesia, there was no evidence of renal dysfunction. To unravel this mystery, two hypotheses put to rest the notion that the circulating inorganic plasma fluoride concentration was nephrotoxic. The first identified the primary isozyme responsible for the degradation of enflurane, isoflurane, sevoflurane, and methoxyflurane anesthetics to be CYP450 2E1 [279, 293–295]; with secondary contributions from CYP450 2A6 and 3A [293]. Large quantities of CYP450 2E1 were found not only within the liver (where degradation of ether inhalational agents yielded large plasma concentrations of inorganic fluoride) but surprisingly within the kidneys [91]. However, the affinity of renal CYP450 2E1 for methoxyflurane was five-fold greater than that for sevoflurane, which resulted in large intrarenal concentrations of inorganic fluoride with the former, damaging the renal tubules and causing a diuresis, whereas with the latter, intrarenal concentrations were small and renal dysfunction did not occur [91]. The second mechanism addressed the metabolic pathway for methoxyflurane, which uniquely included O-demethylated to dichloroacetic acid and inorganic fluoride, causing not only a diuresis but also renal tubular cell necrosis. With methoxyflurane's greater affinity for CYP450 2E1 than sevoflurane and its O-demethylation to dichloroacetic acid, nephrotoxicity after the former anesthetic was far more serious than after the latter [91, 296].

Sevoflurane may also indirectly affect renal function through by-products of *in vitro* metabolism in the presence of carbon dioxide absorbents, for example, soda lime. Five by-products have been identified with two that are potentially nephrotoxic compounds: Compounds A and B. Compound A is produced in concentrations that may be toxic in rats (not in humans), whereas B does not reach toxic concentrations. Nonetheless, the FDA in the USA set the minimum fresh gas flow with sevoflurane to 2 L per minute for >2.5 MAC-h exposure, although this becomes a moot point if absorbents devoid of sodium hydroxide and potassium hydroxide (e.g., Amsorb®) are used (see below). Despite this federal recommendation, low fresh gas flows (<2 L per minute) with sevoflurane are widely used clinically in infants and children and have yet to yield any reports of renal insufficiency [297].

Hepatic

In vivo metabolism of inhalational agents matures with age, increasing within the first two years of life and reaching adult values after this time. The developmental changes in metabolism may be attributed to several factors including reduced activity of the hepatic microsomal enzymes, reduced fat stores, and more rapid elimination of inhalational agents in infants and children compared with adults. Halothane, isoflurane, enflurane, sevoflurane, and desflurane have all been associated with postoperative liver dysfunction and/or failure [298–302]. A recent prospective study in adults concluded that the incidence of drug-induced liver injury from desflurane and sevoflurane in adults was a surprising 4% [303]. Comparable studies in infants and children have not been forthcoming. Halothane and sevoflurane have also been associated with transient hepatic dysfunction in infants and children, but not in neonates [304–306]. Several case reports of transient postoperative liver failure and one case of fulminant hepatic failure and death have been attributed to "halothane hepatitis" that were confirmed serologically to antibodies to halothane-altered hepatic cell membrane antigens in children [304]. The exact mechanism of the hepatic dysfunction after halothane remains unclear, although some have speculated that it is caused by an immunologic response to a metabolite of halothane. This putative toxic metabolite, a trifluoroacetyl halide compound, is produced during oxidative metabolism of halothane. It is believed that this compound induces an immunologic response in the liver by binding covalently to hepatic microsomal proteins, thereby forming an immunologically active hapten. A subsequent exposure to the inhalational agent then incites an immuno-

logic response in the liver [307]. Hepatic enzymes may also be induced by previous administration of drugs such as barbiturates, phenytoin, and rifampin. Although some have admonished clinicians of the risks of repeat anesthetics with halothane and sevoflurane in children, given the millions of uneventful repeat inhalational anesthetics in infants and children worldwide, there is insufficient evidence at present to admonish this practice in neonates and infants.

Clinical Effects

Induction Techniques

Physico-chemical characteristics of the ether series of anesthetics would predict that anesthesia could be induced smoothly and more rapidly with these agents than with halothane (Table 3.1) [175, 176]. However, this has not proved to be the case. All methyl ethyl ether anesthetics irritate the upper airway in children, resulting in a high incidence of breath-holding, coughing, salivation, excitement, laryngospasm, and hemoglobin oxygen desaturation [184, 260, 308–310]. Consequently, most clinicians avoid inhalational inductions with these anesthetics.

In contrast to the irritant airway effects of the methyl ethyl ether anesthetics, the methyl isopropyl ether anesthetic, sevoflurane, is well tolerated when administered by mask to infants and children at any concentration [185, 191, 311–315]. The incidence of coughing, breath-holding, laryngospasm, and hemoglobin oxygen desaturation during inhalational inductions with sevoflurane, whether by slow incremental increases in concentration or a single breath, is similar to those that occur during inductions with halothane. The observation that the airway reflex responses are infrequent after a single breath induction with 8% sevoflurane or 5% halothane casts doubt on the adage that high concentrations of inhalational agents trigger airway reflex responses [313]. In fact, the induction is so smooth with sevoflurane even in neonates that dialing 8% sevoflurane in one step is routine to achieve rapid induction of anesthesia in the neonate without triggering airway reflexes. By increasing the inspired concentration in one step, the period of excitement or agitation during induction is minimized.

Both intravenous and inhalational agents have been used for induction of anesthesia in neonates with congenital heart disease. Sevoflurane compares favorably with halothane for induction of anesthesia in such patients scheduled for cardiac surgery and may be preferred because it maintains cardiovascular stability to a greater extent than halothane, but similar to isoflurane [316–318].

Central Neuroexcitation

Paroxysmal increases in blood pressure (both systolic and diastolic pressures) and heart rate have been reported in adults after a rapid increase in the inspired concentration of isoflurane or desflurane [319–322]. Neuroexcitatory responses have not been reported in neonates with either of these agents nor have they been reported during sevoflurane or halothane anesthesia at any age [321]. This rapid increase in the inspired concentration of isoflurane or desflurane triggers a massive sympathetic response, mediated by norepinephrine and/or epinephrine, resulting in tachycardia and hypertension [322]. Further increases in the inspired concentration of the inciting agent will not control these hyperdynamic responses, but rather will perpetuate or possibly augment the excitatory responses. To restore normal vital signs, the inciting agent must be discontinued and replaced with another inhalational or intravenous agent. Repetitive small increases (1%) in the inspired concentration of the putative agent produce transient, although attenuated catecholamine bursts and cardiovascular responses compared with larger increases in concentrations [323, 324]. Fentanyl (2 μg/kg), esmolol, and clonidine have all been effective in preventing, attenuating, or eliminating these sympathetic responses [325]. The site or sites responsible for triggering a neuroexcitatory response are unknown, although the rapidity of the response suggests that the lung is a primary site [326]. Others however dispute this notion contending that two sites must be responsible for triggering the sympathetic discharge; the lung and a vessel-rich organ [327]. Of these two sites, the vessel-rich organ is believed to mediate the greater response [327].

Emergence

Emergence or recovery has been arbitrarily divided into early (extubation, eye-opening following commands) and late (drinking, discharge time from recovery or hospital). Although most studies have demonstrated a more rapid early recovery after less soluble anesthetics [261, 310, 328, 329] few have demonstrated a more rapid late recovery with these anesthetics than the more soluble anesthetics [183, 185, 330, 331]. Clinicians have been at a loss to explain why neonates/infants with pyloric stenosis recover slowly after a pure inhalational anesthetic. In theory, they should recover rapidly based on the rapid washout of the sevoflurane; however, this has not been our collective clinical experience.

The speed of recovery from anesthesia should follow the order of washout of the inhalational agents: desflurane > sevoflurane > isoflurane > halothane > methoxyflu-

rane [178]. Those agents with lower solubility in blood and tissues are eliminated more rapidly than those with greater solubility; the contribution of metabolism to recovery is minor, because the relative rate of metabolism is small compared with the duration of exposure to anesthetics. This is true for desflurane, which is associated with a more rapid recovery in infants than after sevoflurane [332, 333]. Although some advocate switching inhalational agents from a more soluble to less soluble agent toward the end of surgery for economy and to facilitate a rapid emergence, the only evidence suggests that switching from isoflurane to desflurane 30 min before the end of anesthesia in adults does not speed emergence [334]. However, these results were based on one specific set of clinical conditions in adults that may not apply to all conditions or to neonates and children.

The incidence of complications, such as airway reflex responses and vomiting during emergence from anesthesia, is similar for all inhalational agents [261, 311, 330, 331, 335]. In the case of neonates, airway reflex responses are very common, whereas vomiting after anesthesia is not.

Emergence Delirium

The introduction of the new inhalational agents, desflurane and sevoflurane, has rekindled interest in a clinical entity known as "emergence delirium." Emergence delirium is defined as a dissociated state of consciousness in which a child is inconsolable, irritable, uncompromising, and/or uncooperative. The child is often demanding that all monitors and all bandages be removed and that they are dressed in their clothes. Parents who witness this transient state, which lasts, on average, 10–20 min and occurs primarily in preschool-age toddlers, usually volunteer that this behavior is unusual and uncustomary for their child [336]. However, emergence delirium is rare and unreported in neonates. The incidence of emergence delirium after isoflurane, sevoflurane, and desflurane appears to be similar, but significantly greater than after halothane [329, 337, 338].

The etiology of emergence delirium is unknown. Although pain was initially thought to be responsible for triggering this disorder, a report of a high incidence of delirium after sevoflurane anesthesia for MRI established that pain was not the primary causative agent of delirium after these newer anesthetics [339]. The diagnosis of delirium after inhalational anesthesia was bolstered by the introduction of the Pediatric Anesthesia Emergence Delirium (PAED) scale [340], although this scale has not been validated in neonates. Several preventative measures and interventions have been proposed for the child with delirium after anesthesia [341].

Neuromuscular Junction

Inhalational agents potentiate the actions of nondepolarizing muscle relaxants [342–344] and decrease neuromuscular transmission [345], the latter, however only at large concentrations. The mechanism of the reduced neuromuscular transmission is unknown but may arise from the depression of the central nervous system. The mechanism of the potentiation of nondepolarizing muscle relaxants by inhalational agents is also unknown but is likely attributable to the actions of inhalational agents at the neuromuscular junction rather than pharmacokinetic or central nervous system effects. The potentiation of action of nondepolarizing relaxants follows the order: isoflurane ≈ desflurane ≈ sevoflurane > enflurane > halothane > N_2O/opioid technique [346]. However, this potentiation may depend on the type of nondepolarizing relaxant with longer-acting relaxants affected to a greater extent than intermediate-acting relaxants [347] and the concentration of inhalational agents (in a direct dose-dependent manner). During 0.6 MAC isoflurane, the first twitch recovered to 75% of baseline in 56 min after 0.45 mg/kg rocuronium and 100 min after 0.6 mg/kg [348].

Malignant Hyperthermia (MH)

All inhalational anesthetics (except Xenon) trigger MH reactions in susceptible patients [349]. To date, MH has not been reported in a neonate. Nonetheless, neonates with a family history of MH should be managed with MH precautions. For the most recent management of MH susceptible patients, the reader is referred to the MHAUS website (www.MHAUS.org) or the local national MH website.

Stability

Inhalational agents may be degraded via one of several pathways in the presence of most CO_2 absorbents to form several potentially toxic by-products. Enflurane, isoflurane, and desflurane (but not halothane and sevoflurane) react with dessicated soda lime to produce carbon monoxide. Both halothane and sevoflurane may be degraded when incubated with some CO_2 absorbents, yielding compounds that are potentially organ toxic (see Canizarro reaction below) [350]. Two new absorbents may address these clinical risks: molecular sieves [351] and absorbents lacking sodium and potassium accelerants (e.g., Ambsorb™) [352–355]. Amsorb™ absorbs CO_2 without releasing carbon monoxide or compound A [352, 353]. Carbon dioxide absorbents differ in their composition

and, therefore, in their affinity to interact with inhaled agents. Soda lime contains 95% calcium hydroxide, either sodium or potassium hydroxide, and the balance as water. Baralyme contains 80% calcium hydroxide, 20% barium hydroxide, and the balance as water, but is no longer available due to the flammability risks [356]. Amsorb™ contains 70% calcium hydroxide, 0.7% calcium chloride, 0.7% calcium sulfate, 0.7% polyvinylpyrrolidine, and the balance as water. Amsorb™ and other nonreactive absorbents contain neither sodium nor potassium hydroxide, compounds added to improve CO_2 absorption efficiency [353].

Carbon monoxide may be released into the anesthetic breathing circuit when isoflurane or desflurane is incubated with a desiccated CO_2 absorbent. The absorbent within a CO_2 canister may become desiccated if dry fresh gas flows through the canister at a rate sufficient to remove most of the moisture (i.e., >5 L per minute continuously through the absorbent canister for 24h or greater while it is not in service). If the circuit reservoir bag is detached from the canister, then gas flows through the canister and exits through two possible sites: the smaller fraction of the fresh gas exits through the inspiratory limb of the canister and the larger fraction flows retrograde through the canister and exits at the site where the reservoir bag should be attached. If the reservoir bag is attached to the canister, then limited gas flows retrograde through the canister and the absorbent is unlikely to desiccate. However, once the absorbent becomes desiccated, carbon monoxide will be released into the inspiratory limb of the breathing circuit if one of the methyl ethyl ether inhalational agents (desflurane, isoflurane, or enflurane) is administered [357, 358]. The magnitude of the carbon monoxide production follows the order from greatest to least: desflurane ≥ enflurane > isoflurane ≫ halothane = sevoflurane. Other factors that determine the magnitude of the carbon monoxide concentration produced include the concentration of the inhalational agent, the dryness of the absorbent, the type of absorbent, and the temperature of the absorbent [357]. Currently, carbon monoxide is not detectable by most freestanding anesthetic agent analyzers, pulse oximeters, or blood/gas analyzers (except for cooximeters), although it is detectable by mass spectrometry. The key to this problem is prevention: turn off the anesthetic machine at the end of the day, disconnect the fresh gas hose to the absorbent canister, always leave the reservoir bag connected to the canister, and avoid contact between potentially desiccated absorbent and the three ether anesthetics, desflurane, enflurane, and isoflurane. Others have suggested that high flow anesthesia should be avoided whenever a circle circuit is used to prevent inadvertent desiccation of absorbent. If the absorbent is desiccated, then some recommend "rehydrating" the absorbent, although this too is fraught with potential problems (including clumping of the absorbent) [359]. If one suspects that the absorbent is desiccated, then we recommend replacing the absorbent before introducing an inhalational agent. Alternatives to conventional absorbents such as the molecular sieve and Amsorb™ may very well obviate all reactions that occur with current absorbents [352, 353]. When these same ether anesthetics are incubated with desiccated Amsorb™, carbon monoxide is not produced [352, 353]. Carbon monoxide poisoning is an extremely rare but potentially devastating event during anesthesia when soda lime is used as the CO_2 absorbent. In contrast, the frequency of carbon monoxide poisoning with Amsorb™ is zero.

Sevoflurane is both absorbed and degraded via the Canizarro reaction in the presence of soda lime absorbent, resulting in five degradation products [360]. Although the degradation of sevoflurane by the absorbent was initially posited to delay the wash-in of sevoflurane, recent evidence suggests that the quantity of sevoflurane degraded is of limited clinical significance to the speed of wash-in of sevoflurane [361]. Of the five degradation products between sevoflurane and soda lime, compounds A and B appear in the greatest concentrations in the inspired limb of the breathing circuit, compounds C, D, and E are present in such low concentrations in the breathing circuit that they do not merit further consideration. Compound A, fluoromethyl-2,2-difluoro-1-(trifluoromethyl) vinyl ether (also known as PIFE), is nephrotoxic in rats at concentrations ≥100 ppm and has an LC_{50} of 1100 ppm. Compound B, a methoxyethyl ether compound that is minimally volatile at room temperature, is present in closed circuits at <5 ppm and poses little risk to animals and humans. In a low-flow (≤2 lpm) closed-circuit model with an inspired concentration of 2.5% sevoflurane (up to 3.6 MAC-h) or end-tidal concentration of 3% for 8h, the concentration of compound A peaks at 20–67 ppm after several hours of anesthesia without demonstrable evidence of renal tubular dysfunction [361–364]. Furthermore, low flow sevoflurane (<2 lpm) has not been shown to exacerbate renal dysfunction in patients with pre-existing renal dysfunction (serum creatinine > 1.5 mg/dL) [365, 366]. In children, compound A concentrations are ≤16 ppm after 5.6 MAC•h sevoflurane in a closed circuit with 2 L per minute fresh gas flow [367]. Factors that are known to increase the production of compound A include an increase in the inspired concentration of sevoflurane, Baralyme > soda lime, ventilation, carbon dioxide production, and temperature of the absorbent [368, 369].

Studies in rats indicate that under low flow conditions, compound A is nephrotoxic [370]. In contrast, similar studies in humans have yielded inconsistent results [361–363, 371]. The mechanism behind compound A-induced nephrotoxicity is believed to be ß-lyase-dependent metabolism to nephrotoxic fluorinated compounds, although this has been the subject of intense debate [372]. More recent evidence suggests that differences in the evidence of nephrotoxicity from compound A in rats and humans relate to differences in metabolic pathways between species [373, 374].

Analgesic Drugs

Acetaminophen (Paracetamol)

Mechanism of Action

Acetaminophen is widely used in the management of pain but lacks anti-inflammatory effects. Acetaminophen has a central analgesic effect that is mediated through the activation of descending serotonergic pathways. Prostaglandin H_2 synthetase (PGHS) is the enzyme responsible for the metabolism of arachidonic acid to the unstable prostaglandin H_2. The two major forms of this enzyme are the constitutive PGHS-1 (COX-1) and the inducible PGHS-2 (COX-2). PGHS is comprised of two sites: a cyclooxygenase (COX) site and a peroxidise (POX) site. The conversion of arachidonic acid to PGG_2, the precursor of the prostaglandins (Fig. 3.21), depends on a tyrosine-385 radical at the COX site. Formation of a ferryl protoporphyrin IX radical cation from the reducing agent Fe^{3+} at the POX site is essential for the conversion of tyrosine-385 to its radical form. Acetaminophen acts as a reducing cosubstrate on the POX site and reduces the availability of the ferryl protoporphyrin IX radical cation (Fig. 3.22). This effect can be reduced by the presence of hydroperoxide-generating lipoxygenase enzymes within the cell (peroxide tone) or by swamping the POX site with substrate such as PGG_2. Peroxide tone and swamping explain acetaminophen's lack of peripheral analgesic effect, platelet effect, and anti-inflammatory effects. Alternatively, acetaminophen effects may be mediated by an active metabolite (p-aminophenol). P-aminophenol is conjugated with arachidonic acid by fatty acid amide hydrolase to form AM404. AM404 exerts its effect through cannabinoid receptors [375].

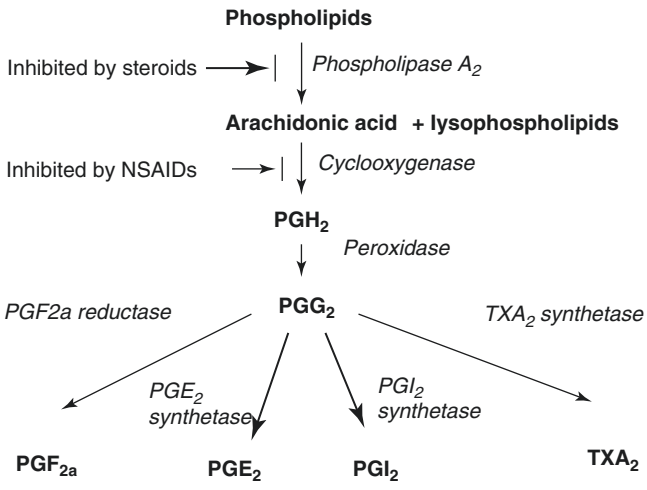


Fig. 3.21 Phospholipid metabolism to the prostaglandins

Analgesic Pharmacodynamics

The ED_{50} for rectal acetaminophen to avoid any supplemental opioids after ambulatory surgery is 35 mg/kg [376]. Time delays of approximately one hour between peak concentration and peak effect have been reported [377, 378]. Pain fluctuations, pain type, and placebo effects complicate interpretation of the clinical studies. A maximum effect of 5.17 (the greatest possible pain relief (VAS 0-10) would equate to an Emax of 10) and an EC_{50} of 9.98 mg/L are reported for pain after tonsillectomy. The equilibration half-time ($T_{1/2}$keo) of the analgesic effect compartment was 53 min [377]. A target effect compartment concentration of 10 mg/L was associated with a pain reduction of 2.6/10 [377]. Similar parameters have been estimated in neonates [379].

Poor analgesic effect after oral and rectal acetaminophen formulations for painful procedures [380, 381], after circumcision [382] and during heel prick [383] are reported. These poor analgesic effects in neonates may be attributable to inadequate serum concentrations (attributable to slow enteral absorption), type of pain stimulus, or assessment tools for the discrimination of pain. Intravenous paracetamol has been successfully used for neonatal analgesia [384].

Pharmacokinetics

The relative bioavailability of rectal to oral acetaminophen formulations ($F_{rectal/oral}$) is approximately 0.5 in children, although the relative bioavailability in neonates is greater, approaching unity [32]. Acetaminophen has a pKa of 9.5 and in the alkaline medium of the duodenum, it is nonionized. Consequently, the absorption half-time of the nonionized form from the duodenum is rapid in children ($T_{1/2}$abs 4.5 min) when it was given as an elixir [385]. The absorption half-time in infants under the age of 3 months was delayed ($T_{1/2}$abs 16.6 min), consistent with delayed gastric emptying in young infants [32, 385]. Rectal absorption is slow and erratic with large variability. For example, absorption parameters for the triglyceride base were $T_{1/2}$abs 1.34 h (CV 90%) with a lag time of 8 min (31%) before absorption began. The absorption half-life for rectal formulations in infants less than three months of age was 150% greater than in older children [72].

Sulfate metabolism is the dominant route of elimination in neonates, while glucuronide conjugation (UGT1A6) is dominant in adults. Glucuronide/sulfate ratios range from 0.12 in preterm neonates of 28–32 weeks PCA, 0.28 in those at 32–36 weeks PCA [386], and 0.34 in full-term neonates <2 days old [387]. A total body clearance of 0.74 L/h/70 kg at 28 weeks PMA and 4.9 (CV 38%) L/h/70 kg in full-term neonates after enteral acetaminophen has been reported using an allometric 3/4 power model [72, 388]. Clearance increases during the first year after birth, reaching 80% of

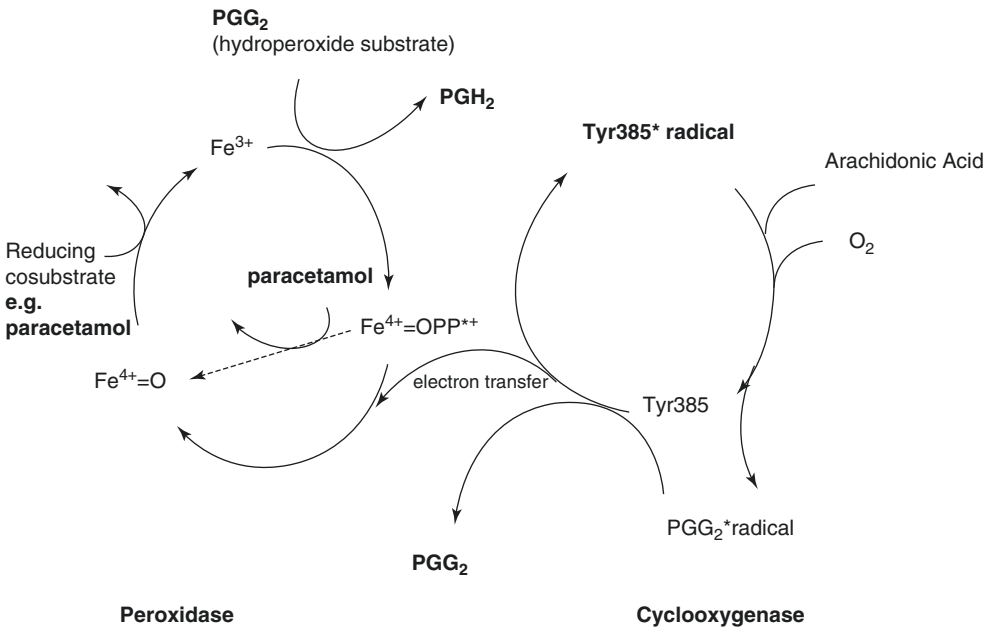


Fig. 3.22 Prostaglandin H_2 synthetase (PGHS) is the enzyme responsible for metabolism of arachidonic acid to the unstable prostaglandin H_2. Formation of tyrosine-385 radical (Tye385*) at the COX site is dependent on the reduction of a ferryl protoporphyrin IX radical cation (Fe^{4+} = OPP*+) at the POX site. Paracetamol is a reducing cosubstrate that partially reduces Fe^{4+} = OPP*+, decreasing the amount available for regeneration of Tyr385*. Figure adapted from Aronoff et al. [215].

that in older children by six months of age (Fig. 3.12) [32, 69]. Similar clearance estimates are reported in neonates after intravenous formulations of acetaminophen (Fig. 3.12) [389, 390]. The relative bioavailability of the oral formulation is 0.9.

The volume of distribution for acetaminophen is (49–70 L/70 kg). The volume of distribution decreases exponentially with a maturation half-life of 11.5 weeks from 109.7 L/70 kg at 28 weeks postconception to 72.9 L/70 kg by 60 weeks [32], reflective of fetal body composition and water distribution changes over the first few months of life (Fig. 3.6).

Adverse Effects

The toxic metabolite of acetaminophen, N-acetyl-p-benzoquinone imine (NAPQI), is formed by the cytochrome P450s CYP2E1, 1A2, and 3A4. This metabolite binds to intracellular hepatic macromolecules to produce cell necrosis and damage. Expression of CYP2E1 activity in vitro is decreased in infants less than 90 days PNA compared with that in older infants, children, and adults [61]; CYP3A4 appears during the first week after birth, whereas CYP1A2 appears later [62]. Neonates can produce hepatotoxic metabolites (e.g., NAPQI), but the reduced activity of cytochrome P-450 in neonates may explain the rare occurrence of acetaminophen-induced hepatotoxicity in neonates [390]. Nonetheless, careful attention must be paid to dosing guidelines as several reports of massive acetaminophen overdose have been reported in neonates [391–393].

Two European centers have published intravenous dosing guidelines for acetaminophen in neonates [394, 395], with the drug used widely by anesthetists in the UK [396]. However, the daily doses differed two-fold in the two studies despite both reporting satisfactory analgesia. Hence, it seems safer to recommend the smaller dosing regimen in neonates. Variability in the clearance and the lack of a suitable marker of reduced clearance in the neonate during the first few days after birth also support recommending the smaller dosing regiment [397]. A larger dose has been advocated, for example, when the PMA is between 32 and 44 weeks, such as a loading dose of 20 mg/kg IV followed by a maintenance dose of 10 mg/kg every 6 h to achieve steady-state plasma concentrations associated with reasonable analgesia. The interval between two maintenance doses should be increased to up to 12 h for infants with a PMA between 28 and 31 weeks [398]. In older infants and children, the recommended IV maintenance dose is 15 mg/kg every 6 h.

Preliminary data from neonates suggest that current dosing regimens are safe [390, 399]. It must be stressed, however, that these are preliminary data only. The combined subject numbers were only 239 neonates. These numbers were too few to exclude the possibility of future hepatotoxicity; caution and continued monitoring of neonates given acetaminophen is vital.

Nonsteroidal Anti-Inflammatory Drugs

Mechanism of Action

Nonsteroidal anti-inflammatory drugs (NSAIDs) are a heterogeneous group of compounds that share common antipyretic, analgesic, and anti-inflammatory properties. NSAIDs act by reducing prostaglandin biosynthesis through inhibition of cyclo-oxygenase (COX) site of the PGHS enzyme. The prostanoids produced by the COX-1 isoenzyme protect the gastric mucosa, regulate renal blood flow, and

induce platelet aggregation. NSAID-induced gastrointestinal toxicity, for example, is likely mediated through blockade of COX-1 activity, whereas the anti-inflammatory effects of NSAIDs are likely mediated primarily through inhibition of the inducible isoform, COX-2.

Pharmacodynamics

The NSAIDs are commonly used in children for antipyresis and analgesia. The anti-inflammatory properties of the NSAIDs have also been used in diverse disorders such as juvenile idiopathic arthritis, renal and biliary colic, dysmenorrhoea, Kawasaki disease, and cystic fibrosis. The NSAIDs indomethacin and ibuprofen are also used to treat delayed closure of patent ductus arteriosus (PDA) in preterm infants.

There are no linked PK-PD studies of NSAID analgesia or fever in neonates or infants. Investigation of a concentration-response relationship for PDA closure shows that a target serum concentration of 3.5 mg/L is associated with 90% PDA closure. Dosing increases with PMA to achieve this target, because clearance increases with age [400]. Concentration-response relationships for pain have been described in children and adults. The maximum effect (Emax) for both diclofenac and ibuprofen was similar (5/10 VAS) to that described for acetaminophen, although the $T_{1/2}$keo was smaller (20–30 min), suggesting quicker onset of effect [401]. The onset of analgesia may correlate with CSF concentrations. CSF penetration by ketorolac, diclofenac, ibuprofen, and indomethacin is rapid in children; peak concentrations reached ~30 min after intravenous administration of routine doses [402–405].

Pharmacokinetics

NSAIDs are rapidly absorbed in the gastrointestinal tract after oral administration in children. The relative bioavailability of oral preparations approaches unity. The rate and extent of absorption after rectal administration of NSAIDs such as ibuprofen, diclofenac, flurbiprofen, indomethacin, and nimesulide are less than after the oral routes.

The apparent volume of distribution of NSAIDs in adults is small (<0.2 L/kg), but larger in children. Intravenous ibuprofen has a volume of distribution of 0.62 (S.D. 0.04) L/kg in preterm neonates (22–31 weeks gestational age) [406]. Its central volume is dramatically reduced after closure of the PDA in preterm neonates (0.244 vs. 0.171 L/kg) [407]. The NSAIDs, as a group, are weakly acidic, lipophilic, and highly protein bound. The bound fraction is greater in children and preterm neonates but less than in adults. The impact of altered protein binding is probably minimal with routine dosing, because NSAIDs cleared by the liver have a low hepatic extraction ratio [408].

NSAIDs undergo extensive phase I and phase II enzyme biotransformation in the liver, with subsequent excretion into urine or bile. Renal elimination is not an important elimination pathway for the commonly used NSAIDs. Variability in the pharmacokinetic parameter estimates is large, in part, attributable to covariate effects of age, size, and pharmacogenomics. Ibuprofen, for example, is metabolized by the CYP2C9 and CYP2C8 subfamily. Considerable variation exists in the expression of CYP2C activities among individuals, and functional polymorphism of the gene coding for CYP2C9 has been described [409]. CYP2C9 activity is low immediately after birth (21% of adult), subsequently increasing progressively to reach a peak activity within 3 months when expressed as mg/kg/h [410].

Clearance (L/h/kg) is generally greater in children than it is in adults, as we might expect when a linear per kilogram model is used. Ibuprofen clearance increases from 2.06 mL/h/kg at 22–31 weeks PCA [406], 9.49 mL/h/kg at 28 weeks PCA [407] to 140 mL/kg/min at 5 years [411]. Similar data exist for indomethacin [412–414]..

Many NSAIDs exhibit stereoselectivity [415]. Ibuprofen stereoselectivity is reported in preterm neonates (<28 weeks gestation). R- and S-ibuprofen half-lives were about 10 h and 25.5 h, respectively. The mean clearance of R-ibuprofen (12.7 mL/h) was about 2.5-fold greater than for S-ibuprofen (5.0 mL/h) [416].

During pregnancy, there is relatively little transfer of NSAIDs from maternal to fetal blood. Very small quantities of NSAIDs are secreted into breast milk, for example, ketorolac in breast milk is estimated to be 0.4% of maternal exposure [417].

Ketorolac (Toradol) is an NSAID with very potent analgesic properties that can be administered intravenously [418]. Ketorolac has been safely used to provide analgesia for preterm and term infants, although the PK in this age group has not been described [419]. A major concern with ketorolac is that it inhibits platelet function through inhibition of cyclooxygenase, which increases the risk of postsurgical bleeding. There is a dose-response relationship for this bleeding risk; a greater and clinically important risk is associated with larger doses, older subjects, and durations greater than 5 days [420]. Ketorolac can be used to treat pain after congenital heart surgery (median age 10 months, range 2.5–174), without an increased risk of bleeding complications [421].

Drug Interactions

NSAIDs undergo drug interactions through altered clearance and competition for active renal tubular secretion with other organic acids. A high fractional protein binding has been proposed to explain drug interactions between NSAIDs and oral anticoagulant agents, oral hypoglycemics, sulfonamides, bilirubin, and other protein-bound drugs.

An additive effect from combination therapy between acetaminophen and an NSAID has been reported in children [422, 423]. Although the maximum effect was unchanged with combination therapy (Emax 5/10, VAS 0-10), the dura-

tion of effect was prolonged beyond that observed for either drug alone.

Adverse Effects

NSAIDs have the potential to cause gastrointestinal irritation, blood clotting disorders, renal impairment, neutrophil dysfunction, and bronchoconstriction, effects that are attributed to the COX-1/COX-2 ratios, although this concept may be an oversimplification.

Ibuprofen reduces the GFR by 20% in preterm neonates, affecting aminoglycoside clearance, an effect that appears to be independent of gestational age [95]. No significant difference in cerebral blood volume, cerebral blood flow, or tissue oxygenation index was found between the administration of ibuprofen or placebo in neonates [424].

The risk of acute GI bleeding in children given short-term ibuprofen was estimated to be 7.2/100,000 (CI 2-18/100,000) [425, 426], a prevalence similar to that in children given acetaminophen. The incidence of clinically significant gastropathy in children given NSAIDs for JIA is comparable with that in adults given long-term NSAIDs in children given NSAIDs for JIA [427, 428], but the prevalence of gastroduodenal injury may be very much greater depending on the assessment criteria (e.g., abdominal pain, anemia, endoscopy) applied. Data from neonates are not available.

The commonly used NSAIDs have reversible antiplatelet effects, which are attributable to the inhibition of thromboxane synthesis. Bleeding time is usually slightly increased but remains within normal limits in children with normal coagulation systems. The frequency of intraventricular hemorrhage in neonates who were given prophylactic ibuprofen to close the PDA was unchanged [429].

Opioid Analgesic Drugs

Morphine

Morphine is among the most commonly used opioid in neonates and infants. Morphine's main analgesic effect is by supraspinal μ_1-receptor activation. The μ_2-receptor in the spinal cord plays an important analgesic role when the drug is administered by the intrathecal or epidural route [430]. Morphine is soluble in water, but lipid solubility is poor compared with other opioids. Morphine's limited oil/water partition coefficient, 1.4, and its pKa of 8 (10–20% unionized drug at physiologic pH) contribute to delayed onset of peak action with slow CNS penetration.

Pharmacodynamics

Target analgesic plasma concentrations are believed to be 10–20 ng/mL after major surgery in neonates and infants [78, 431]. The concentration required for sedation during mechanical ventilation may be greater (125 ng/mL) [432]. The large pharmacokinetic and pharmacodynamic variability suggests that morphine is often titrated to effect using small incremental doses (0.02 mg/kg) in neonates and infants suffering postoperative pain [433, 434]. The effect compartment equilibration half-time ($T_{1/2}$keo) for morphine is ~17 min in adults [435] and is estimated to be 8 min in the full-term neonate [436]. The role of morphine for nursing procedures in the neonatal unit remains controversial. Morphine did not reduce pain responses during endotracheal suctioning, despite plasma concentrations up to 400 ng/mL [71].

The principal metabolites of morphine, morphine-3-glucuronide (M3G), and morphine-6-glucuronide (M6G) have pharmacologic activity. Contributions to both the desired effect (analgesia) and the undesired effects (nausea, respiratory depression) of M6G are the subject of clinical controversy [437]. It has been suggested that M3G antagonizes morphine and contributes to the development of tolerance [438].

Pharmacokinetics

Oral bioavailability is ~35% due to this first-pass effect. Morphine is primarily metabolized by the hepatic enzyme UGT2B7 into M3G and M6G. Sulfation and renal clearance are minor pathways in adults but are more dominant in neonates. Clearance is perfusion limited with a high hepatic extraction ratio. The metabolites are cleared by the kidney and, in part, by biliary excretion. M3G and M6G accumulate in the presence of impaired renal function.

Morphine clearance matures with PMA reaching adult values at 6–12 months [71]. Clearance increases from 3.2 L h^{-1}.70 kg^{-1} at 24 weeks PMA to 9.3 L.h^{-1}.70 kg^{-1} at 32 weeks PMA in and 19 L.h^{-1}.70 kg^{-1} at term (Fig. 3.12). The volume of distribution is increased in preterm ventilated neonates (190 L.70 kg^{-1}) compared with full-term neonates who were breathing spontaneously (122 L.70 kg^{-1}) [71]. The volume of distribution in term neonates increased from 83 L/70 kg at birth to a mature value of 136 L/70 kg within 3 months. Metabolite (M3G, M6G) clearance increases with age similar to that described for GFR maturation in infants [70].

Morphine dosing in neonates can be estimated using clearance estimates (Fig. 3.23). Although an infusion of 5 mcg/kg/h will achieve a target concentration of 10 ng/mL in a typical neonate at term, clearance is affected by PMA and pathology. Morphine pharmacokinetic parameters show large interindividual variability contributing to the range of morphine serum concentrations observed during constant infusions. Protein binding of morphine is small in preterm neonates and has minimal impact on the disposition changes with age. The M6G/morphine ratio also changes with age (Fig. 3.24) because of the desynchrony between the maturation of metabolite formation and elimination pathways, but the clinical effect of these ratio changes is unclear.

Although morphine is usually administered intravenously to neonates, other routes have been used. Rectal administra-

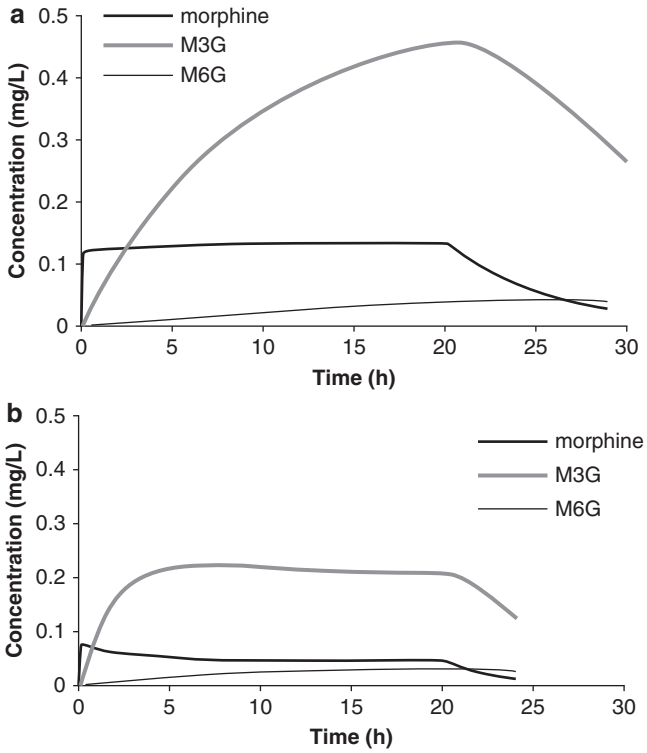


Fig. 3.23 Morphine administered as a bolus 0.07 mg/kg with subsequent infusion 0.03 mg/kg/h in a neonate (**a**) and a 1-year-old child (**b**). The concentrations of parent drug and metabolites are different in the two individuals because of the complex interplays between formation and elimination clearances. (Data from Bouwmeester NJ, Anderson BJ, Tibboel D, Holford NH. Developmental pharmacokinetics of morphine and its metabolites in neonates, infants and young children. Br J Anaesth. 2004;92:208–17) [70]

tion of morphine results in a large variability in the analgesia conferred, which is a major disadvantage of this route. Although the rectal route is commonly used [439], delayed absorption after multiple doses leading to respiratory arrest has been reported [440]. Morphine (25–50 mcg/kg) can also be given via the caudal route to neonates [441, 442]. While systemic absorption is slow, morphine spreads within the CSF to the brainstem where it may cause respiratory depression lasting from 6 h to >18 h [443].

Adverse Effects

Respiratory depression may occur at concentrations of 20 ng/mL [53] in infants and children, but concentration-response relationships in neonates, particularly preterm neonates prone to physiological apnea, are unknown. Hypotension, bradycardia, and flushing reflect morphine's histamine-releasing characteristics. These are more pronounced with rapid intravenous bolus administration [444, 445]. The incidence of vomiting in postoperative children is related to the dose of morphine: doses >0.1 mg/kg are associated with a >50% incidence of vomiting in infants and children [446, 447]. It is difficult to quantify this adverse effect in awake healthy neonates who commonly regurgitate after feeding.

Withdrawal symptoms may be observed in neonates after cessation of a continuous morphine infusion for >2 weeks and after infusion periods <2 weeks if the morphine infusion rate is >40 μg/kg/h. Strategies to prevent withdrawal from morphine include the use of neuraxial analgesia, nurse-controlled sedation management protocols, ketamine or naloxone mixed with morphine infusion, and the use of alternate agents (e.g., methadone) with reduced potential for tolerance [448, 449].

Fentanyl

Fentanyl offers greater hemodynamic stability than morphine, a rapid onset ($T_{1/2}$keo = 6.6 min in adults) and a short duration of effect. Its relative increased lipid solubility and small molecular conformation enables efficient penetration of the BBB and redistribution.

Pharmacodynamics

Fentanyl is a potent μ-receptor agonist with a potency 70–125 times greater than that of morphine. A plasma concentration of 15–30 ng/mL is required to provide total intravenous anesthesia (TIVA) in adults, whereas the EC_{50}, based on EEG evidence, is 10 ng/mL [450, 451]. Fentanyl has been shown to effectively prevent preterm neonates from surgical stress responses and to improve postoperative outcome [452]. Single doses of fentanyl (3 mcg/kg) can reduce the physiologic and behavioral measures of pain and stress associated with mechanical ventilation in preterm infants [453]. Fentanyl has similar respiratory depression in infants and adults in the presence of comparable plasma concentrations [454].

Pharmacokinetics

Fentanyl is metabolized by oxidative N-dealkylation (CYP3A4) into nor-fentanyl and hydroxylated. All metabolites are inactive, and a small amount of fentanyl is eliminated via the kidneys unchanged. Fentanyl clearance is 70–80% of adult values in term neonates and, when standardized to a 70-kg person, reaches adult values (approx. 50 L/h/70 kg) within the first 2 weeks of life [46]. Clearance matures with gestational age: 7 mL/min/kg at 25 weeks PMA, 10 mL/min/kg at 30 weeks PMA, and 12 mL/min/kg at 35 weeks PMA [455]. Fentanyl's volume of distribution at steady state (Vss) is ~5.9 L/kg in term neonates and decreases with age to 4.5 L/kg during infancy, 3.1 L/kg during childhood, and 1.6 L/kg in adults [42]. This increased Vss results in a smaller blood concentration after bolus administration in neonates and infants. Administration of fentanyl 3 mcg/kg in infants intraoperatively neither depresses respiration nor causes hypoxemia in a placebo-controlled trial [456, 457].

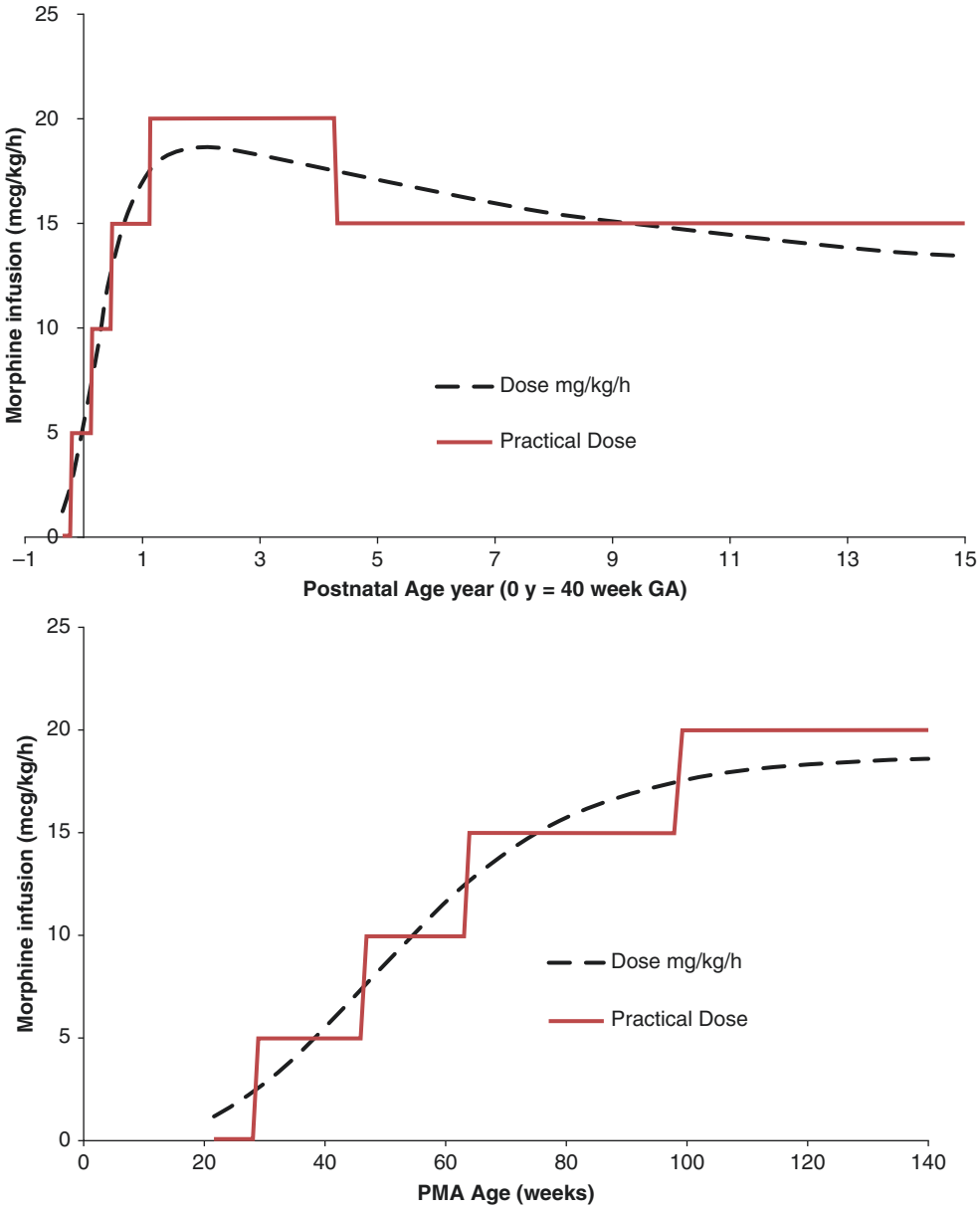


Fig. 3.24 Age-based infusion dosing for morphine with a target average steady-state concentration of 10 mcg/L in children not receiving positive pressure ventilation. The dotted line is the predictions based on age and typical weight for age. The solid line is the suggested practical infusion rate dose in mcg/kg/h at different postnatal ages. PNA years = (PMA weeks − 40)/52. The upper panel shows dose related to postnatal age. The lower panel shows dose related to PMA. From Anderson BJ. Arch Dis Child 2013; 98: 732–6, with permission

Fentanyl clearance may be impaired with decreased hepatic blood flow, for example, from increased intra-abdominal pressure in neonatal omphalocele repair. Infants with cyanotic heart disease exhibit a reduced Vss and greater plasma concentrations of fentanyl with infusion therapy [458]. These greater plasma concentrations result from a reduced clearance (34 L/h/70 kg), that was attributed to hemodynamic disturbance and consequent reduced hepatic blood flow [459].

Fentanyl is widely distributed with a short duration of effect as a result of redistribution to deep, lipid-rich compartments. Fentanyl redistributes slowly from lipid-rich tissues after discontinuation of therapy, resulting in prolonged periods of sedation and respiratory depression. Although CYP3A4 is subject to single nuclear polymorphisms with slow and rapid metabolizers, their contribution to the metabolism of fentanyl is small. Redistribution rather than clearance is responsible for offset of the drug effect after single-dose therapy. The context-sensitive half-time (CSHT) after a 1 h infusion of fentanyl is ~20 min, which increases to 270 min after an 8 h infusion in adults [460]. While the CSHT is reduced in children [461], there are no data in neonates.

Alternative administration routes (e.g., transdermal and transmucosal) have not been studied in neonates, although intranasal fentanyl has been used for palliative care in neonates [462, 463]. Epidural fentanyl is widely combined with an amide local anesthetic for postoperative analgesia, although there is no evidence that fentanyl is required as usual concentrations of local anesthetics in children are

100% effective [464]. Though spread beyond the spinal level of administration is dose dependent, respiratory depression is uncommon [465, 466].

Adverse Effects

Neonatal tolerance to synthetic opioids develops more rapidly (3–5 days) than it does with morphine (2 weeks) and diamorphine (>2 weeks) [3, 467]. Fentanyl also has a propensity to cause muscular rigidity and laryngospasm in neonates with doses as small as 2 mcg/kg IV [468, 469]. Other drugs metabolized by CYP3A4 (e.g., cyclosporin, erythromycin) may compete for clearance and increase fentanyl plasma concentrations.

Respiratory depression (hours) may outlast fentanyl's analgesic effect (35–45 min) due to the prolonged CSHT and/or recirculation of fentanyl bound to the gastric acid medium (up to 20% of an iv dose) or delayed release from peripheral compartments.

Remifentanil

Remifentanil resembles fentanyl, sufentanil, and alfentanil in chemical structure. It is a selective μ-receptor agonist with a greater potency than alfentanil. Its brief elimination half-life of 3–6 min [83, 470] means it is usually given as an infusion [471, 472]. Intravenous remifentanil doses of 0.25 μg/kg/min appear to be safe and effective in neonates [473, 474].

Pharmacodynamics

A target plasma concentration of remifentanil of 0.2–0.4 mcg/L is adequate for analgesia, 2–3 mcg/L for laryngoscopy, 6–8 mcg/L for laparotomy, and 10–12 mcg/L might be sought to ablate the stress response associated with cardiac surgery [475]. The $T_{1/2}$keo of 0.64–1.16 min in adults [2, 83] decreases with age. Analgesic alternatives should be available when the short-duration analgesic effect from remifentanil has dissipated. Reports of a rapid development of μ-receptor tolerance with remifentanil use are conflicting. Activity at δ-opioid receptors may contribute [476].

Pharmacokinetics

Remifentanil is metabolized by nonspecific esterases in tissues and erythrocytes to carbonic acid [477, 478] and these esterases appear to have mature function even in preterm neonates [24]. Carbonic acid is excreted via the kidneys. Metabolism is independent of liver and renal functions. Clearance in patients with butyryl-cholinesterase deficiency is unaffected.

Remifentanil clearance can be described in all age groups by the simple application of an allometric model [479]. This standardized clearance of 2790 mL/min/70 kg is similar to that reported by others in children [84, 480] and adults [83, 477]. The smaller the child, the greater the clearance when expressed as mL/min/kg. These estimates have been confirmed over an even greater age range (5 days to 85 years, weight range 2.5 to 106 kg) [2]. Clearance decreases with age, with rates of 90 mL/kg/min in infants <2 years of age, 60 mL/kg/min in children 2 to 12 years of age, and 40 mL/kg/min in adults [81, 479, 480]. The steady-state volume of distribution was greatest in infants <2 months age (452 mL/kg) and decreased to 308 mL/kg in children 2 mo-2 y and to 240 mL/kg in children >2 y [83]. Elimination half-life appears to be constant: ~3 to 6 min independent of the age of the patient and duration of the infusion [83, 470]. Intravenous remifentanil doses of 0.25 μg/kg/min appear to be safe and effective in neonates [473, 474], although PK-PD data in this age group remain limited [2].

Although covariate effects such as cardiac surgery appear to have a muted effect on PK, as is seen with propofol, cardiopulmonary bypass (CPB) does have an impact. Remifentanil dose adjustments are required during and after CPB due to marked changes in its volume of distribution [481]. Other PK changes during CPB are consistent with adult data in which a decreased metabolism occurred with a reduced temperature [482] and with reports of greater clearance after CPB (increased metabolism) compared with during CPB [480].

Adverse Effects

Respiratory depression is concentration dependent [483, 484]. Muscle rigidity is a concern with bolus doses >3 mcg/kg, but not 2 μg/kg during intubation in neonates [485, 486]. The initial loading dose of remifentanil may cause hypotension and bradycardia [487], prompting some to target the plasma rather than effect-site concentration when initiating infusion. This hypotensive response has been quantified in children undergoing cranioplasty surgery. A steady-state remifentanil concentration of 14 mcg/L would typically achieve a 30% decrease in MAP. This concentration is twice that required for laparotomy, but is easily achieved with a bolus injection. The $T_{1/2}$keo of 0.86 min for this hemodynamic effect [488] is less than remifentanil-induced spectral edge changes described in adults ($T_{1/2}$keo = 1.34 min) [82, 489]. Neonatal data are very limited.

Because the inhibitory neurotransmitter, glycine, is included in the formulation of remifentanil, it should not be used for spinal or epidural applications [490].

Alfentanil

Alfentanil is a synthetic opioid that is chemically related to fentanyl. It has a rapid onset ($T_{1/2}$keo = 0.9 min in adults), a brief duration of action, and one-fourth the potency of fentanyl. Alfentanil has reduced lipid solubility and causes less histamine release than fentanyl [491]. The analgesic dose of

alfentanil for tracheal intubation and suctioning in preterm neonates is 10–20 μg/kg [492–494]. A target plasma concentration of 400 ng/mL is used in anesthesia. Metabolism is through oxidative N-dealkalation by CYP3A4 and O-dealkalation and then conjugation to end-products that are excreted via the kidney [495]. The plasma protein binding of alfentanil increases from 65% in preterm neonates to 79% in term infants and then to ~90% in adults [496, 497]. The volume of distribution (Vss) in children (0.163 L/kg) is one-third that in adults (0.457 L/kg) [498]. Clearance in neonates (20–60 mL/min/70 kg) is one-tenth that in adults (250–500 mL/min/70 kg) [499]. In preterm neonates, the elimination half-life ranges is 6–9 h, 4–5 fold greater than in infants and children [500, 501]. Alfentanil cannot be used without neuromuscular-blocking drugs in neonates because of the frequency of rigidity [492, 502].

Sufentanil

Sufentanil is 5–10 times more potent than fentanyl, with a $t_{1/2}$keo of 6.2 min in adults [503]. A concentration of 5–10 ng/mL is required for TIVA and 0.2–0.4 ng/mL for analgesia. Pharmacodynamic differences are suggested in neonates. The plasma concentration of sufentanil at the time of additional anesthetic supplementation to suppress hemodynamic responses to surgical stimulation was 2.51 ng/mL in neonates, notably greater than the concentrations of 1.58, 1.53, and 1.56 ng/mL observed in infants, children, and adolescents, respectively [504].

Elimination of sufentanil has been suggested by O-demethylation and N-dealkylation in animal studies. Like fentanyl and alfentanil, the P-450 CYP3A4 enzyme is responsible for the N-dealkylation [505]. Clearance in neonates undergoing cardiovascular surgery (6.7 (SD 6.1) mL/kg/min) is reduced compared with values of 18.1 (SD 2.7), 16.9 (SD 3.2), and 13.1 (SD 3.6) mL/kg/min in infants, children, and adolescents, respectively [504]. Clearance rates in infants (27.5 (SD 9.3) mL/kg/min) were greater than those in children (18.1 (SD 10.7) mL/kg/min) in another study of children undergoing cardiovascular surgery [506]. Maturation of clearance is rapid [507] and clearance maturation, standardized to a 70-kg person using allometry, is similar to that of other drugs that depend on CYP3A4 for metabolism (e.g., levobupivacaine, fentanyl, alfentanil) (Fig. 3.12) [508]. The volume of distribution at steady state (Vss) was 4.15 (SD 1.0) L/kg in neonates, greater than the values of 2.73 (SD 0.5) and 2.75 (SD 0.5) L/kg observed in children and adolescents, respectively [504, 509]. Clearance in healthy children (2–8 years) was greater (30.5 (SD 8.8) mL/kg/min) than those undergoing cardiac surgery [509]. Decreased hepatic blood flow reduces clearance [509].

The free fraction of sufentanil decreases with increasing age (neonates 19%; infants 11%; children and adults 8%) and is strongly correlated with the alpha 1-acid glycoprotein plasma concentration [496]. The reduced concentration of alpha 1-acid glycoprotein in neonates and infants increases the free fraction of sufentanil in these age groups. Although sufentanil, fentanyl, alfentanil, and remifentanil have >70% protein binding and have high hepatic (or nonhepatic for remifentanil) extraction ratios, protein-binding changes are probably clinically unimportant [510], because the dose is titrated to effect, and variability in the clearance has a much greater impact.

Epidural sufentanil (0.7–0.75 mcg/kg) has been effective in children lasting >3 h [511–513], although pruritus can be bothersome [511]. Nasal sufentanil may have a role for sedation in children although data in neonates are lacking [514–516].

Codeine

Codeine, or methylmorphine, is a morphine-like opioid with 1/10 the potency of morphine. It is primarily metabolized by glucuronidation, with secondary (minor) pathways including N-demethylation to norcodeine and O-demethylation to morphine. Approximately 10% of codeine is metabolized to morphine. As the affinity of codeine for opioid receptors is very low, the analgesic effect of codeine is mainly due to its metabolite, morphine [517]. Codeine is effectively a prodrug analgesic. The continued use of this minor opium alkaloid to treat perioperative analgesia in infants and children has remained baffling in light of it being a prodrug, although reports of fatal consequences after use in children have resulted in its use being severely restricted or proscribed in pediatrics in many jurisdictions [518].

The CYP2D6 enzyme catalyzes the metabolism of codeine to morphine. A genetic polymorphism of this enzyme causes distinct phenotypes responsible for the presence of ultrarapid (UM), extensive (EM), and slow or poor (PM) codeine metabolizers [519, 520]. Between 7% and 10% of Europeans are PM of codeine [520–522], depending on race [520, 521]. PM do not benefit from pain relief from codeine, although its side effects persist [522], whereas UM amass very large concentrations of morphine that may lead to an alarming frequency of adverse side effects including apnea.

Codeine can be administered by intramuscular, oral, and rectal routes. Intravenous codeine is not recommended because of hypotensive effects [523]. Blood concentrations after rectal codeine are less than those after intramuscular codeine, because the rectal route results in incomplete, slower, and more variable absorption [524]. Codeine is often combined with acetaminophen or NSAIDs to improve post-

operative pain relief in infants [525] and children [526, 527]. Maturation of CYP2D6 follows that of M1 production from tramadol (Fig. 3.10), a metabolite also produced by CYP2D6. This enzyme matures rapidly after 40 weeks PMA, suggesting that postterm neonates could benefit, although this drug has not been investigated in neonates. Several deaths or near-deaths have been reported after codeine use in children subsequently identified as UM [528, 529]. Codeine use in neonates and children has been strongly discouraged ever since [530].

The pharmacokinetics of codeine is poorly described in children despite several decades of use. A volume of distribution (V) of 3.6 L/kg and a clearance (CL) of 0.85 L/h have been described in adults, but there are few data of the developmental changes in pediatric pharmacokinetics. The half-life in neonates (4.5 h) is greater than that in infants (2.6 h) as a result of immature clearance [531]. Administration (especially of codeine preparations with an antihistamine and a decongestant) in the neonate may cause intoxication [532]. One fatal event occurred in a neonate that was attributed to morphine poisoning after his mother used codeine while breastfeeding. The mother, an UM, produced much more morphine than most adults, and it was purportedly transferred to the neonate [533, 534].

The adverse effects of codeine are broadly similar to those of other opioids. Adverse effects at small doses are directly related to the plasma concentrations of morphine, but are caused by codeine at greater doses [535]. There is a broad belief that codeine causes fewer adverse effects, such as sedation and respiratory depression, compared with other opioids, but this belief is not evidence based. The analgesic effect of codeine depends on its conversion to morphine. Consequently, when other, nonopioid medications compete for the CYP2D6 enzyme (e.g., quinidine), the analgesic effect of codeine may be attenuated.

Meperidine (Pethidine)

Meperidine is a weak opioid, primarily μ-receptor, agonist that has a potency of 1/10 that of morphine. In adults, the analgesic effects are detected within 5 min of intravenous administration, with the peak effect reached within 10 min [536, 537]. Meperidine is metabolized by N-demethylation to meperidinic acid and normeperidine. Meperidine clearance in infants and children is approximately 8–10 mL/min/kg [502, 538] The elimination half-life in neonates is greatly reduced compared with older children and elimination half-time in neonates who have received meperidine by placental transfer is 2–7 times greater than that in adults [539]. The Vss in infants, 7.2 (3.3–11) L/kg [502], is greater than that in children 2–8 years of 2.8 (SD 0.6) L/kg [538].

Meperidine was initially synthesized as an anticholinergic agent but was soon discovered to have analgesic properties. Although meperidine's anticholinergic effects were demonstrated *in vitro*, the anticholinergic effects on the biliary and renal tracts have not been demonstrated *in vivo*. Studies have demonstrated that meperidine is no more effective for treating biliary or renal tract spasm than comparable μ opioids [540]. Because morphine results in better analgesia with fewer side effects, there are no particular advantages of meperidine as an analgesic [541]. Accumulation of the metabolite normeperidine may cause seizures and dysphoria [542], although the metabolism of meperidine to normeperidine is reduced 7-fold in neonates compared with adults [539].

Intramuscular administration of meperidine was frequently used in pediatric patients in the past, but this route is generally avoided today because it is painful and may lead to sterile abscesses. Meperidine was used for several years as a component of various "lytic cocktails" that provided sedation in infants and children. It was administered either rectally or orally. The safety of these admixtures, especially in neonates, is not evidence based and, consequently, is used infrequently [543]. Meperidine's local anesthetic properties have been found useful for epidural techniques [544].

Methadone

Methadone is a synthetic opioid with an analgesic potency similar to that of morphine but with a more rapid distribution and a slower elimination. Methadone is used as a maintenance drug in opioid-addicted adults to prevent withdrawal. Methadone might have beneficial effects, because it is a long-acting synthetic opioid with a very high bioavailability (80%) by the enteral route. It also has NMDA receptor antagonistic activity. Agonism of this receptor is associated with opioid tolerance and hyperalgesia. Methadone is a racemate with clinical effects attributed to the R-methadone isomer. Methadone is 2.5–20 times more analgesic than morphine [545].

Although only limited data on the efficacy and safety of methadone are available, methadone is widely used for the treatment of opioid withdrawal (neonatal abstinence syndrome) in neonates and children [448, 546, 547]. Methadone treatment reduces the length of stay for abstinence syndrome by 22% compared with morphine in full-term neonates, although a recent systematic review failed to establish the superiority of either medication [548, 549]. Intravenous methadone is also an effective analgesic for postoperative pain relief [550], and oral administration has been recommended as the first-line opioid for severe and persistent pain in children [551]. It is also safe as an enteral alternative for intravenous opioids in palliative pediatric oncological patients [552]. Although some have proposed that metha-

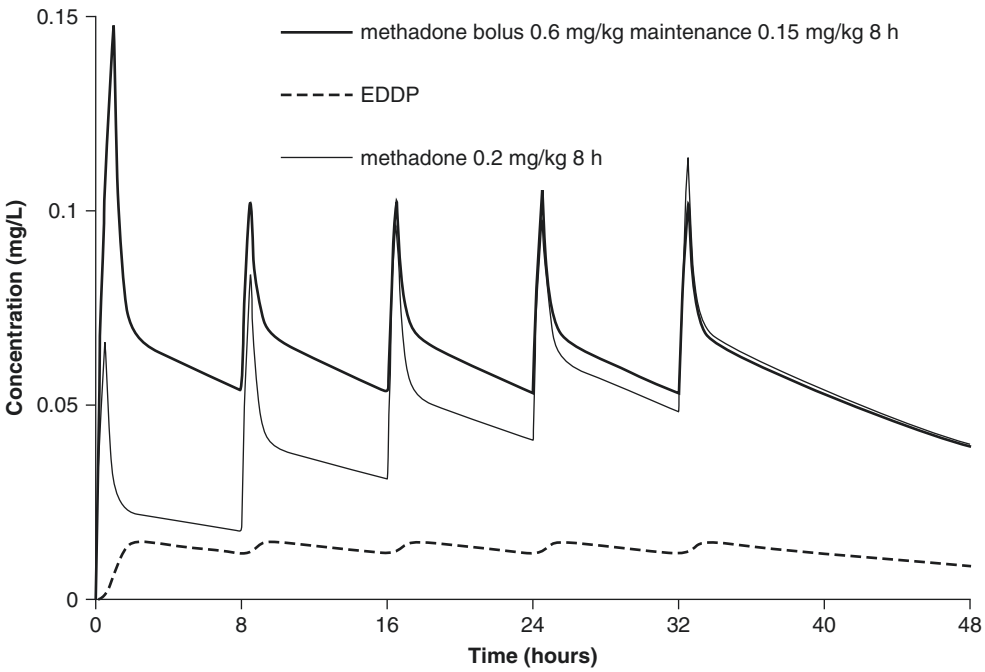


Fig. 3.25 Simulation for a 3.5-kg neonate given a methadone loading dose of 0.6 mg/kg followed by a maintenance dose of 0.15 mg/kg 8 h. EDDP concentrations track parent drug concentrations. The methadone target concentration of 0.06 mg/L is achieved rapidly when compared to the neonate given 0.2 mg/kg 8 hourly without a loading dose. From Ward RM, Drover DR, Hammer GB, Stemland CJ, Kern S, Tristani-Firouzi M, Lugo RA, Satterfield K, Anderson BJ. The pharmacokinetics of methadone and its metabolites in neonates, Infants and children. Pediatr Anesth 2014: 591–601, with permission [23]

done should assume a predominant role in the management of prolonged pain in neonates, its role in this regard needs to be evaluated in a clinical research setting [449].

Methadone has a high lipid solubility [553] with a large volume of distribution in children and adults [554–556]. Pharmacokinetic parameters, standardized to a 70 kg adult using allometry, have been estimated using a three-compartment linear disposition model. Population parameter estimates (between subject variability) were central volume (V1) 21.5 (29%) L/70 kg, peripheral volumes of distribution V2 75.1 (23%) L/70 kg, V3 484 (8%) L/70 kg, clearance (CL) 9.45 (11%) L/h/70 kg and intercompartment clearances Q2 325 (21%) L/h/70 kg, Q3 136 (14%) L/h/70 kg [23]. These parameter estimates in children and neonates are consistent with those reported by others in neonates, children, adolescents, and adults [557–559]. The clearance of methadone does not mature with age, because CYP3A7 is active in neonates before maturation of CYP3A4, which plays a primary role in clearance later in life. Neonatal enantiomer clearances were also similar to those described in adults [23]. The major metabolite 2-ethylidene-1,5-dimethyl-3,3-diphenylpyrrolidine (EDDP) is often measured in urine as part of a drug abuse testing program.

The target concentration for both opioid withdrawal in neonates and analgesia in adults is 0.06 mg/L. An intravenous regimen of 0.2 mg/kg 8 h in neonates achieves a target concentration of 0.06 mg/L within 36 h (Fig. 3.25). Analgesic response in adults on chronic methadone programs suggests a steep concentration-response relationship for pain relief (Hill = 4.4) with very rapid equilibration between plasma methadone concentrations and the sites mediating pain relief. Consequently, the drug rapidly loses effect as concentrations decrease to less than EC_{50}. It should be noted that methadone, like other opioids, has large between-subject PK variability that could result in drug accumulation and possible fatal outcomes with long-term administration [560].

Sedatives

Benzodiazepines

These drugs produce anxiolysis, amnesia, and hypnosis. They are commonly used as adjuncts to both local and general anesthesia. Currently, midazolam is the most commonly used benzodiazepine in the perioperative period. It is water soluble in an acid pH carrier, but becomes lipid soluble at physiological pH, which facilitates rapid BBB entry. Midazolam is highly bound to serum albumin (>96%). Midazolam is a medium extraction drug and changes in the plasma protein concentrations will not affect clearance. However, a reduced albumin concentration will increase the unbound fraction after bolus intravenous administration.

Mechanism of Action

Benzodiazepines bind to $GABA_A$ receptors, increasing chloride entry into cells. This hyperpolarizes the $GABA_A$ receptors, rendering them resistant to excitation.

Pharmacodynamics

PKPD relationships have been described for intravenous midazolam in adults. When an EEG signal is used as an effect measure, the EC_{50} is 35–77 ng/mL, with a $T_{1/2}$keo of 0.9–1.6 min [561–563]. The $T_{1/2}$keo is increased in the

elderly and in low cardiac output states, but estimates in neonates are lacking. Decreased clearance in neonates means that the duration of effect persists despite decreasing the plasma concentrations (Fig. 3.26) [564]. PKPD relationships are more difficult to describe after oral midazolam, because the active metabolite, 1-hydroxy metabolite (1-OHMDZ), has approximately half the activity of the parent drug [565].

Sedation in children is more difficult to quantify. PKPD relationships were not established in children (aged 2 days–17 years) who were given a midazolam infusion in intensive care. Midazolam dosing could, however, be effectively titrated to the desired level of sedation, using the COMFORT scale [566]. Consistent with this finding, desirable sedation in children after cardiac surgery was achieved at mean serum concentrations between 100 and 500 ng/mL [567–569].

Pharmacokinetics

Midazolam is metabolized mainly by hepatic hydroxylation (CYP3A4) [58]. These hydroxymetabolites are glucuronidated and excreted in the urine. CYP3A7 is the dominant CYP3A enzyme *in utero*; it is expressed in the fetal liver and appears to have activity from as early as 50–60 days postconception. There appears to be a temporal switch in the immediate perinatal period with the expression of CYP3A4 increasing dramatically after the first postnatal week. Hepatic CYP3A4 activity begins to increase dramatically at about 1 week PNA, reaching 30–40% of adult expression by 1 month [508]. Midazolam clearance does not parallel CYP3A4 activity, because clearance also depends on the size of the liver, its blood flow, and environmental factors. Midazolam has a hepatic extraction ratio in the intermediate range 0.3–0.7. Metabolic clearance depends on both liver perfusion and enzyme activity.

Clearance in neonates is reduced (0.8–2.2 mL/min/kg) [570–575], but increases exponentially after 39 weeks PMA [573, 576]. Central volume of distribution is related to weight (V1 0.591 SD 0.065 L/kg), whereas peripheral volume of distribution remains constant (V2 0.42 SD 0.11 L) in 187 neonates 0.7–5.2 kg [573]. It has been suggested that midazolam self-induces its clearance [567]. The latter observation from infants after cardiac surgery likely results from the improved hepatic function after the insult of cardiopulmonary bypass. Neonates who require extracorporeal membrane oxygenation (ECMO) have an increase in Vss during ECMO therapy (0.8 L/kg to 4.1 L/kg) caused by sequestration of midazolam by the circuitry, although clearance (1.4 SD 0.15 mL/min/kg) was unchanged [577].

Clearance may be reduced in the presence of pathology. The clearance of midazolam is reduced after circulatory arrest for cardiac surgery [578]. Covariates such as renal failure, hepatic failure [569], and concomitant administration of CYP3A inhibitors [579] are important predictors of altered midazolam and metabolite pharmacokinetics in pediatric intensive care patients [580]. The clearance of midazolam was reduced by 30% in neonates receiving sympathomimetic amines, probably as a consequence of the underlying compromised hemodynamics [573].

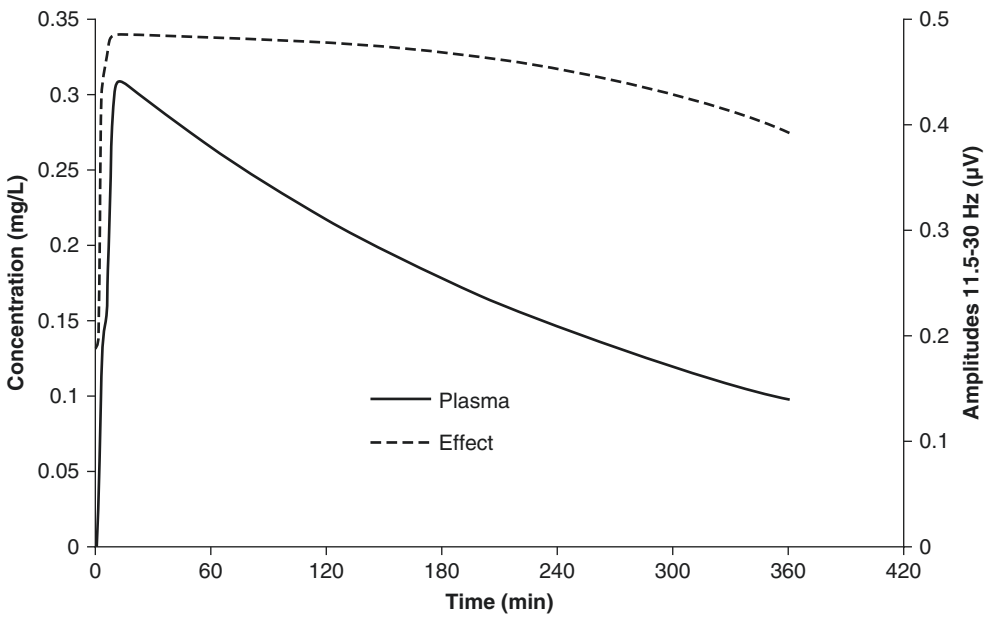


Fig. 3.26 Plasma concentrations and effect in a neonate given protocol midazolam bolus (0.1 mg/kg) on two early occasions (5 min interval) to achieve sedation. Plasma concentration declines slowly because of slow clearance. Sedation recovery lags way behind the decline in plasma concentration even though a maintenance infusion was not even given. Pharmacodynamic parameter estimates were from Mandema J et al. Pharmacokinetic-pharmacodynamic modeling of the central nervous system effects of midazolam and its main metabolite alpha-hydroxymidazolam in healthy volunteer. Clin Pharm Ther 1992;51:715–28 [561]. From Wolf A, Blackwood B, Anderson BJ. Tolerance to sedative drugs in PICU: Can it be moderated or is it immutable? Intensive Care Medicine 2016; 42(2):278–81 [564]

Adverse Effects

Metabolites can accumulate in the presence of renal failure, causing increased sedation. Respiratory depression and hypotension after midazolam are well recognized. Cessation of long-term sedation with midazolam can cause withdrawal symptoms often manifest as irritability, agitation, tremors, and sleeplessness.

Alpha-2 agonists

Clonidine

Clonidine is an alpha-2 adrenoreceptor agonist that produces sedation, anxiolysis, analgesia, and hypotension. It is commonly administered in the caudal and epidural space where it prolongs the duration of analgesia approximately 3 h [581–583].

Pharmacodynamics

The plasma concentration of clonidine that provides analgesia in adults is 1.5–2 mcg/L [584–586]. Clonidine-mediated analgesia, sedation, and anxiolysis are dose dependent in adults [587–589]. The target concentration for analgesia in adults is greater than that for sedation. To achieve satisfactory preoperative sedation with clonidine in children 1–11 years, a plasma concentration of 0.3–0.8 mcg/L is required [590]. The concentration required for 50% of children to achieve a sedation scale of 4 (appears asleep, purposeful responses to verbal commands but at louder than usual conversation level or requiring light glabellar trap) or greater is slightly more, 0.85 μg/L and 90% of children achieve this by 1.15 μg/L. [591] At a concentration of 4 μg/L, levels of general anesthesia are achieved (BIS <60) [584]. When clonidine is added to analgesic regimens [584, 592] at a plasma clonidine concentration of 1.5–2 mcg/L, the morphine use is reduced up to 30% [585, 586].

When administered intravenously at clinically relevant doses, alpha-2 agonists have a biphasic effect on blood pressure but produce a dose-dependent decrease in heart rate. This biphasic effect on blood pressure results from two different sites of alpha-2 adrenoceptor stimulation – an initial direct action on peripheral vascular resistance and a delayed central sympatholysis [593, 594]. The net effect of these responses was a 26.3% reduction in mean arterial blood pressure after intravenous doses of 2.5 mcg/kg in children 1–10 years [595].

Pharmacokinetics

Approximately 50% of clonidine is eliminated unchanged by the kidney and there is considerable interindividual variability [589, 596, 597]. It remains unclear which drug-metabolizing enzymes are responsible for nonrenal clearance. Between 40% and 60% of clonidine after intravenous administration undergoes hepatic biotransformation, although the exact percent is unclear [589, 596–598] The major metabolite of clonidine is p-hydroxyclonidine, formed by hydroxylation of the phenol ring, which is present at <10% of the concentration in the urine [596]. CYP2D6 is involved in this process.

There are limited pharmacokinetic data in neonates and none in preterm neonates. A pooled pediatric analysis reported the clearance of clonidine at birth to be 3.8 L/h/70 kg (0.12 L/h/kg), a rate that matured with a half-time of 25.7 weeks to reach 82% adult rate by 1 year PNA. The central volume of distribution (V1) was 62.5 (71.1%) L/70 kg, intercompartment clearance (Q) 157 (77.3%) L/h/70 kg, and peripheral volume of distribution (V2) 119 (22.9%) L/70 kg. The volumes of distribution, but not clearance, increased after cardiac surgery. There was a lag time of 2.3 (CV 73.2%) min before absorption began after rectal administration [599]. The absorption half-life from the epidural space was slower than that from the rectum (0.98 CV 24.5% h vs. 0.26 CV 32.3% h). The relative bioavailability of epidural and rectal clonidine was unity ($F = 1$) compared with intravenous administration [600]. A study of 36 neonates (0.5–26 days PNA) given oral clonidine for neonatal abstinence syndrome estimated an apparent clearance of 0.16 L/h/kg [601]., which is consistent with intravenous clearance estimates given probable reduced oral bioavailability; oral bioavailability is 0.55 in children [602].

Dexmedetomidine

Dexmedetomidine has a seven times greater specificity for the alpha-2 adrenoreceptor than clonidine. Dexmedetomidine is a unique alpha-2 adrenoceptor agonist that, unlike traditional sedative agents, is reported to produce its sedative effect, at least in part, through an endogenous sleep-promoting pathway that does not produce clinically significant respiratory depression [603–606]. The use of dexmedetomidine in neonatal intensive care and sedation practice is increasing [607, 608]. Dexmedetomidine use in neonates and children has even expanded to include early extubation after cardiac surgery, prevention of emergence delirium, postoperative pain management, invasive and noninvasive procedural sedation, and the management of opioid withdrawal [603–605, 608–615]

Pharmacodynamics

A plasma concentration greater than 0.6 μg/L produces satisfactory sedation in adult ICU patients [616] and similar target concentrations are estimated in children, but there is a lack of neonatal experience [617]. When administered as a single IV bolus dose in infants after cardiac surgery, dexmedetomidine produces a biphasic effect of mean arterial blood pressure (Fig. 3.27). The peripheral vasopressor effect is directly related to a plasma concentration with an $Emax_{pos}$ of 50.3 (CV 44.50%) mmHg, EC_{50pos} 1.1 (48.27%) μg/L, and a

$Hill_{pos}$ coefficient of 1.65. The delayed central sympatholytic response is described with an $Emax_{neg}$ of -12.30 (CV 37.01%) mmHg, EC_{50neg} 0.10 (104.40%) μg/L, and a $Hill_{neg}$ coefficient of 2.35. The equilibration half-time ($T_{1/2}keo$) is 9.66 (165.23%) min [619]. These results have not been reproduced in children presenting for sedation during radiological procedures. There was a 5% incidence of hypertension in these patients; the incidence was greatest in those less than 1-year of age and those who required an additional bolus dose to maintain sedation [618].

Upper airway changes associated with increasing doses of dexmedetomidine (1–3 μg/kg) in children without OSA are small in magnitude and do not appear to be associated with clinical signs of airway obstruction. Even though these changes are small, all precautions to manage airway obstruction should be taken when dexmedetomidine is used for sedation [620]. Upper airway changes during dexmedetomidine (2 μg/kg/h) compared with propofol sedation yielded similar requirements for airway support [621].

Dexmedetomidine is not associated with neuroapoptosis or other neurodegenerative effects as evident from two animal studies involving infant rodents and fetal primates [622, 623]. Dexmedetomidine also attenuates isoflurane-induced neurocognitive impairment in neonatal rats [624]. A contrary report suggested that dexmedetomidine may have detrimental effects on the brain, but those areas affected differ from other drugs. Ketamine resulted in cellular degeneration and apoptosis in limbic brain regions, but nonsignificant changes in primary sensory brain regions. In contrast, dexmedetomidine produced cellular degeneration and apoptosis in primary sensory brain regions of rat pups, but nonsignificant changes in limbic regions [625]. The bulk of current evidence suggests fewer consequences attributable to α_2-agonists than most other anesthetic drugs. Consequently, the drug is being explored in animal models for possible use in neonates who have suffered perinatal asphyxia. Its neuroprotective, analgesic, anti-inflammatory, and sympatholytic properties may be beneficial when combined with therapeutic hypothermia [626–628].

Pharmacokinetics

Population parameter estimates for a two-compartment model were clearance (CL) 42.1 (CV 30.9%) $L.h^{-1}.70\ kg^{-1}$, central volume of distribution (V1) 56.3 (61.3%) $L.70\ kg^{-1}$, intercompartment clearance (Q) 78.3 (37.0%) $L.h^{-1}.70\ kg^{-1}$, and peripheral volume of distribution (V2) 69.0 (47.0%) $L.70\ kg^{-1}$. Clearance increases from 18.2 $L.h^{-1}.70\ kg^{-1}$ at birth in a full-term neonate to reach 84.5% of the mature value by 1 year PNA (Fig. 3.12). Children given a dexmedetomidine infusion after cardiac surgery had reduced clearance (83.0%) compared with a population given a bolus dose [617]. Others have described similar parameter estimates with reduced clearance in children receiving dexmedetomidine infusion after cardiac surgery [629].

Adverse Effects

Intravenous use for CT scanning has been associated with modest fluctuations in heart rate and blood pressure that required no pharmacologic interventions or reporting as adverse events [630]. Similar results were noted for MRI scanning. Although high-dose dexmedetomidine (≥2 mcg/kg/h) was associated with decreases in heart rate and blood pressure outside the established "awake" normal values for children, the deviations were generally within 20% of normal. Nonetheless, some infants developed profound bradycardias and hypotension. No adverse sequelae were reported [631]. Less favorable results have been noted in the

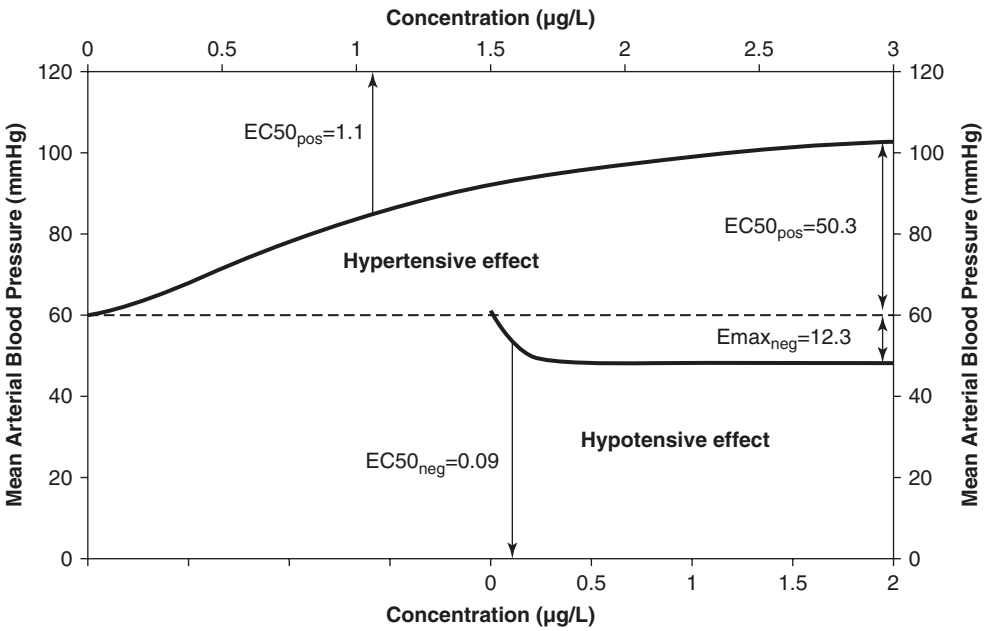


Fig. 3.27 Composite Emax model, showing hyper- and hypotensive effect of dexmedetomidine on mean arterial blood pressure. From Potts A et al. [619]

electrophysiology laboratory. Heart rate decreased while arterial blood pressure increased significantly after 1 mcg/kg IV over 10 min followed by a 10-min continuous infusion of 0.7 mcg/kg/h. Sinus node function was significantly affected and atrioventricular nodal function was also depressed. The use of dexmedetomidine may not be desirable during electrophysiology studies as it may cause bradycardia or atrioventricular nodal block [632].

Local Anesthetic Agents

Mechanism of Action

Local anesthetics are grouped as either amino amides (lignocaine, bupivacaine) or amino esters (prilocaine, tetracaine), although their mechanisms of action are the same. They act principally by inactivating the fast sodium channels that initiate neural action potentials. Inactivation occurs on the cytosolic aspect of the membrane. Drug must first traverse this phospholipid bilayer membrane before exerting an effect. Effect from individual agents depends on the molecular size, lipid solubility, unbound drug availability, and degree of ionization at physiological pH. Neonates have reduced concentrations of AAG, and this increases the unbound concentration [633, 634] compared with adults. A decrease in pH will also increase the unbound concentration in plasma. Neonates with their greater metabolic rate and reduced bicarbonate stores may be more prone to acidosis during convulsions caused by local anesthetic toxicity increasing susceptibility to subsequent cardiac toxicity. A decrease in intracellular pH also causes ion trapping of the active moiety of the local anesthetic molecule, leading to further exacerbation of toxicity [635].

Cardiac sodium channels are more sensitive and stereospecific than nerve channels. Consequently, the R(+) enantiomer of bupivacaine has greater toxicity than the S(−) enantiomer (levobupivacaine) in cardiac myocytes [636]. Local anesthetics also affect potassium and calcium ion channels. Nodal conduction in the heart depends on calcium channel activity and influence at this site can cause dysrhythmias. Neonates have a relative immaturity of the sarcoplasmic reticular regulation of cytosolic calcium, and force development and relaxation in the immature heart depend more on the transsarcolemma calcium flux than in the adult [637].

Unmyelinated fibers are more sensitive to local anesthetic effects than myelinated fibers and myelination is incomplete at birth. Local anesthetics need to block 2–3 adjacent nodes of Ranvier to block conduction in myelinated fibers. Thinly myelinated fibers have shorter distances between nodes than thickly myelinated fibers. Consequently, neonates and infants need only small concentrations of local anesthetic to achieve a similar blockade as that observed in adults.

Pharmacodynamics

Local anesthetics are antiepileptics at reduced concentrations, acting either on GABA-glutamate regulation or by blocking sodium channels like phenytoin. At serum concentrations less than 5–7 μg/mL, lidocaine possesses anticonvulsant properties in infants [638–640]. At concentrations greater than 7–10 μg/mL, lidocaine causes convulsions, while at serum concentrations greater than 15–20 μg/mL, lidocaine induces global depression with coma and cardiovascular collapse.

The effect of local anesthetics on sodium channel preparations is difficult to quantify, because they depend on the type of channel investigated, biochemical and electrophysiological conditions, or stereospecificity [641]. Sodium channels expressed in nerve fibers have an EC_{50} ranging from ~100 μM to 800 μM for lidocaine and to 150 μM for bupivacaine [642–644]. Successful neuronal blockade in vivo requires concentrations 200 times greater, because penetration of the perineural area is poor. Vascular removal and degree of ionization result in only a small amount of drug reaching the sodium channel. Hydrophobic drugs (e.g., bupivacaine) cross into neural tissue more readily than those that are more hydrophilic (e.g., prilocaine)

Levobupivacaine and ropivacaine are less cardiotoxic than bupivacaine. A mean plasma concentration of levobupivacaine in healthy adults of 2.38 mg/L is less cardiodepressive than a bupivacaine concentration of 1.87 mg/L [645], but there are no recommendations regarding the "safe" serum concentration of levobupivacaine in children.

Prilocaine is combined with lignocaine in the EMLA, a eutectic mixture of topical local anesthetic. Neonates tend to form methemoglobin, because they have reduced methemoglobin reductase activity and fetal hemoglobin is more readily oxidized compared with adult hemoglobin. This proclivity, combined with the increased percutaneous absorption, resulted in a reluctance to repeat doses of lidocaine-prilocaine cream in neonates [36], although single dose application is safe [646].

Pharmacokinetics

The major hepatic clearance pathway for lidocaine to its active metabolites monoethylglycinexylidide and glycinexylidide is CYP1A2. Lidocaine is a high extraction drug that displays perfusion limited clearance. Clearance is equivalent to hepatic blood flow and a reduction in hepatic blood flow reduces clearance. The total body clearance of lidocaine in neonates, expressed per kilogram, is similar to that reported in adults (0.55 vs. 0.61 L/h/kg). Although hepatic blood flow is increased in neonates [49], CYP1A2 activity is not detectable until well after birth [59]. CYP3A4, which

has a minor role in lignocaine clearance in adults, is also immature in neonates. CYP3A7 is expressed in the fetal liver and may contribute to clearance. Neonates excrete a greater fraction of the dose unchanged in urine and the urinary metabolites, which account for more than 70% of the dose in adults, account for less than 30% of the dose in neonates [647]. Renal function is also immature in neonates [75] and thus, we might anticipate a reduced clearance of lidocaine in neonates. Allometric scaling reveals a standardized clearance that is one-third that of adults.

CYP3A4 assumes a greater role in the clearance of bupivacaine and levobupivacaine. Bupivacaine is predominantly metabolized into pipecoloxylidide by CYP3A4. Maturation patterns are similar for bupivacaine and levobupivacaine. Levobupivacaine clearance is 5.8 L/h/70 kg at 1-month PNA and increases with a maturation half-time of 2.3 months to reach 80% of the mature value of 22.1 L/h/70 kg by 6-month PNA (Fig. 3.7). Ropivacaine is mainly metabolized into 3′- and 4′-OH-ropivacaine by the CYP1A2 and to a minor extent to pipecoloxylidide by CYP3A4. Maturation of ropivacaine may be slower [59]. An unbound clearance of 120 L/h/70 kg at 30 days PNA is 33% that of the mature estimate for ropivacaine [63, 648]. Clearance is considered capacity limited as the extraction ratio for both bupivacaine and ropivacaine is 35% in adults. Failure to appreciate the reduced clearance of bupivacaine in neonates has resulted in convulsions during continuous epidural infusion [649, 650]. Safe continuous epidural infusion rates of bupivacaine in neonates, 0.2–0.25 mg/kg/h (maximum 72 h) and children, 0.4–0.5 mg/kg/h, were empirically derived [1]. These rates maintain steady-state concentrations of ~1 mg/L and mirror age-related clearance changes for up to 48 h. The volume of distribution of lidocaine in neonates is twice that of adults (2.75 vs. 1.1 L/kg) [647]. Although changes in the volume of distribution of bupivacaine have not been reported with age [651] or with its enantiomers, ropivacaine and levobupivacaine [64, 648, 652], the volume of distribution of unbound ropivacaine increased over the first six postnatal months [653], attributed to a corresponding increase in alpha-acid glycoprotein [651].

In contrast to the amide local anesthetics, esters are rapidly metabolized by plasma cholinesterases. Chloroprocaine is neither protein bound nor does it depend on hepato-renal elimination [654]. Two studies reported their experience with epidural 3% and 1.5% 2-chloroprocaine in neonates and infants [655, 656]. After a loading dose of 1–1.5 mL/kg epidural, effective analgesia was achieved with 1–1.5 mL/kg/h continuous infusion resulting in plasma levels of chloroprocaine of 0–0.5 mg/L.

The clearance of esters in adults, 2.37 L/min, far exceeds the hepatic blood flow, supporting its extensive extrahepatic metabolism [652]. Some patients have reduced plasma concentrations of cholinesterase with consequent reduced clearance of ester local anesthetics. There are a great number of plasma cholinesterases genotypes that lead to wide variations in plasma cholinesterase activity [657].

Disposition may be altered by anatomical differences between infant and child. In neonates and young infants, an epidural catheter can be threaded easily from the caudal space to the thoracic region. Anatomical studies have shown that in neonates and young infants, the epidural fat is spongy and gelatinous in appearance with distinct spaces between individual fat globules [658]. With increasing age, fat becomes more tightly packed and fibrous. Local anesthetics bind to epidural fat. Absorption half-life (T_{abs}) and the time to peak concentration (T_{max}) are increased in this neonatal age group [64]. Reduced clearance and slow absorption both contribute to the observed increase T_{max} (Fig. 3.28). The absorption half-time would be consistent with increased epidural fat rather than reduced epidural fat and the increased T_{abs} may have more to do with the surface area available for absorption in the epidural space.

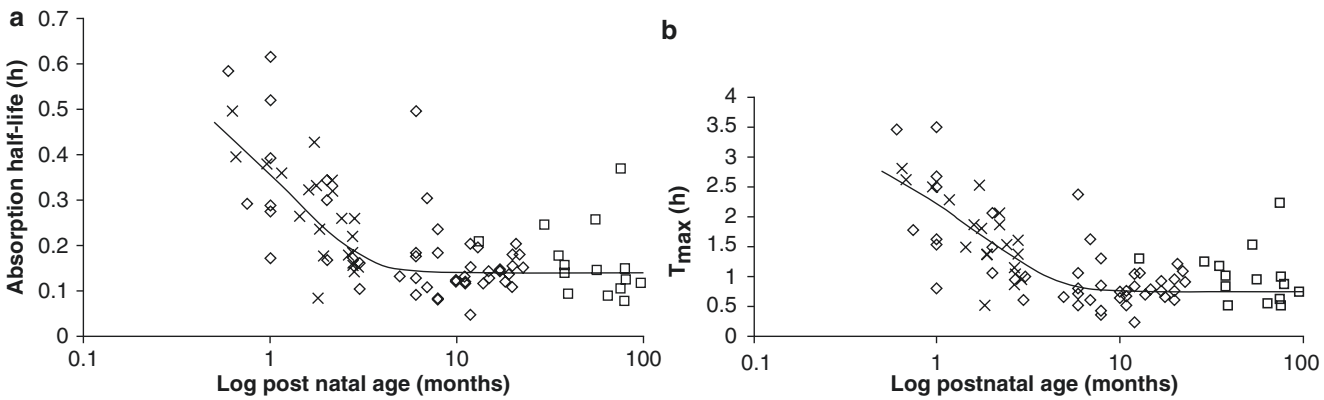


Fig. 3.28 (**a**) Individual predicted levobupivacaine absorption half-time (T_{abs}), standardized to a 70-kg person, are plotted against postnatal age. The solid line represents the nonlinear relation between T_{abs} and postnatal age. (**b**) Individual predicted levobupivacaine time to peak concentration (T_{max}) after 2 mg/kg, standardized to a 70-kg person, is plotted against postnatal age. The solid line represents the nonlinear relation between T_{max} and postnatal age. From Chalkiadis GS et al. [64]

Observations in neonatal lambs with surgically created left-to-right shunts revealed both reduced clearance and volume of distribution of lignocaine [659]. These data are yet to be confirmed in humans.

Adverse Effects

The major adverse effects are related to cardiovascular and central nervous systems. Cardiac toxicity is more commonly reported in children than neurotoxicity, although this may be attributable to masking of neurotoxic symptoms and signs during anesthesia. The use of benzodiazepines may suppress seizure activity, while inhalational drugs may exacerbate cardiovascular signs.

Plasma concentrations of lignocaine from 10 mcg/mL and bupivacaine 3–5 mcg/mL in adults may be expected to produce adverse effects. However, adverse events range in severity and correlate with total concentrations. The rate of plasma concentration, protein binding, ionization, arterial oxygen tension, and maturity of the blood–brain barrier also influence the risk of toxicity. With reduced protein-binding capacity, immature BBB, metabolic acidosis during seizure activity, propensity to desaturate rapidly, and immature cardiac physiology, neonates are at greater risk for adverse effects [660].

Neuromuscular Blocking Drugs

Neonatal Physiology

The neuromuscular junction is immature and structurally different in neonates, skeletal muscle properties change in infancy, the relative proportion of muscle to body weight is reduced, the extracellular fluid that neuromuscular-blocking drugs (NMBDs) distribute to is increased, metabolic clearance pathways are often immature and the relationship between parasympathetic and sympathetic tone unbalanced in early life. Surprisingly, NMBDs behave differently in neonates both in the desired effects and adverse effects.

Fetal neonatal postjunctional acetylcholine receptors differ from receptors in adults [661, 662]. Adult receptors possess five subunits, namely, two α, one β, δ, and ε subunits, whereas neonates (<31 weeks PMA) have a γ-subunit instead of an ε-subunit in their neuromuscular receptor [663]. The opening time of fetal receptors is greater than that in adults, allowing more sodium to enter the cell with a resultant larger depolarizing potential. The resulting increased sensitivity to acetylcholine is at odds with the observed increased sensitivity to NMBDs but may compensate for reduced acetylcholine stores in the terminal nerve endings [664].

Neuromuscular transmission is immature in neonates and infants until the age of 2 months [665, 666]. In response to tetanic nerve stimulation, neonates deplete acetylcholine vesicle reserves more rapidly than infants >2 months old and children [665],. Data from phrenic nerve-hemidiaphragm preparations from rats aged 11–28 days suggests this is due to a low quantal content of acetylcholine in neonatal endplate potentials [109]. Neonates display an increased sensitivity to NMBDs. An alternative proposal to explain this increased sensitivity is based on NMBD synergism observations [667, 668]. Neonates display poor synergism and this has been explained on the basis that NMBDs occupy only one of the two α-subunit receptor sites in neonates as opposed to two in children and adults [668]. If true, then neonates may use NMBDs more efficiently than children.

Skeletal muscle fibers can be grouped into two broad types: type I, slow-contracting fibers are rich in oxidative enzymes, whereas type II, fast-contracting fibers that are rich in glycolytic enzymes. In the neonate, the diaphragm contains only 10% of the type I fibers. This proportion increases to 25% at term and 55% by 2 years of age. This explains, in part, why infants tolerate respiratory loads poorly. A similar maturation pattern is observed for intercostal muscles. Type I fibers tend to be more sensitive to NMBDs than type II fibers and consequently, the diaphragmatic function in neonates may be better preserved and recover earlier than peripheral muscles.

Changes in the ECF in infants (Fig. 3.6) affect the volume of distribution of drugs. Polar drugs such as depolarizing and nondepolarizing neuromuscular-blocking drugs (NMBDs) distribute rapidly into the ECF but enter cells more slowly. The initial dose of such drugs is greater in infants compared with children and adults. Increasing muscle bulk adds new acetylcholine receptors. This greater number of receptors requires a greater amount of drug to block activation of receptor ion channels.

Pharmacodynamics

Age-related variability in the dose required to achieve a predetermined level of neuromuscular blockade has been reported for nondepolarizing NMBDs during balanced thiopental-N_2O-fentanyl anesthesia (Fig. 3.29). The ED_{95} of vecuronium was 47 (SD 11) μg/kg in neonates and infants, 81 (SD 12) μg/kg in children between 3 and 10 years of age, and 55 (SD 12) μg/kg in children aged ≥13 years [670]. Similar profiles have been reported for other NMBDs [669, 671–674]. Furthermore, the duration of neuromuscular blockade is greater in neonates than it is in children [675]. The reduced dose requirement in neonates has been attributed to the immaturity of the neuromuscular junction. The

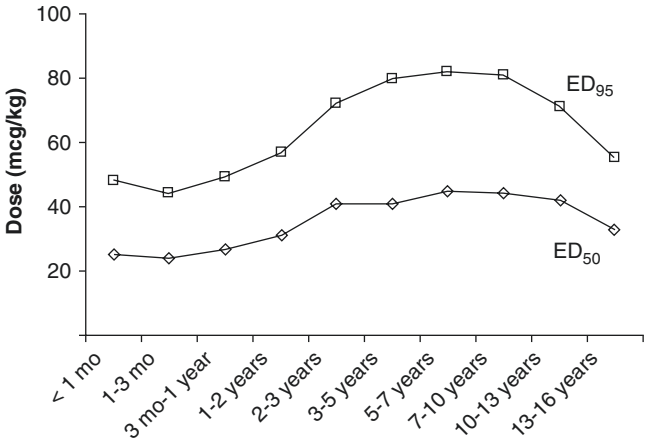


Fig. 3.29 Dose changes with age for vecuronium during balanced anesthesia. ED_{50} is the dose that achieves 50% of the maximum response, while $ED_{95}$is the dose that achieves 95% of the maximum response. Data from Meretoja et al. [669]

increased volume of distribution from an expanded ECF in neonates implies a similar initial dose in neonates and teenagers. The reason for the greater dosing in children compared with adults is unclear, although it could be attributed to increased muscle bulk.

Investigation into the concentration-response relationships is more revealing. The plasma concentration required to achieve the same level of neuromuscular block in neonates as in children or adults is 20–50 % less [676–679], consistent with immaturity of the neuromuscular junction. Plasma concentration requirements are reduced by volatile anesthetic agents [680–682].

The onset time for NMBDs in neonates is faster than it is in older children than adults. Onset time (time to maximal effect) after vecuronium 70 μg/kg was most rapid for infants (1.5 SD 0.6 min compared with that for children (2.4 SD 1.4 min) and adults (2.9 SD 0.2 min) [675]. These observations are similar to those reported for other intermediate- and long-acting NMBDs [683]. The more rapid onset of these drugs in neonates has been attributed to a greater cardiac output based on the per kilogram model [683].

Cardiac output is commonly used as a surrogate measure for muscle perfusion. Onset time is a function of size. An onset time standardized to a 70 kg person using an allometric 1/4 power model is about 3 min. In children with low cardiac output or decreased muscle perfusion, onset times are prolonged. The onset of neuromuscular paralysis is proportional to $T_{1/2}$keo. Increasing the inspired concentration of halothane increases the $t_{1/2}$keo of d-tubocurare [684]. The explanation for the delayed onset of action of tubocurarine may be halothane's negative inotropy [685] and decreased muscle blood flow [686].

Succinylcholine remains the NMBD with the most rapid onset of action. The onset time of a paralyzing dose (1.0 mg/kg) of succinylcholine is 35–55 s in children and adolescents. The onset time after 3 mg/kg in neonates is even faster, 30–40 s [687]. The onset time depends on both age and dose; the younger the child and the greater the dose, the quicker the onset time. The onset times of equipotent doses of succinylcholine (0.9 min) and mivacurium (1.4 min) in infants (2–12 months) and children (1–12 years) are similar [688]. Consequently, an argument can be made for the use of larger doses of an intermediate-duration NMBD rather than succinylcholine for rapid sequence intubation. However, increased doses of such drugs in the neonate will also prolong neuromuscular blockade and increase the risk of adverse effects (e.g., pain on injection, tachycardia). Phase II blockade may also develop with large or repeat doses of succinylcholine [689].

Succinylcholine may be injected intramuscularly for tracheal intubation in children [690]. Few data are available in neonates, but studies in infants suggest that a dose of up to 5 mg/kg may be required to achieve satisfactory intubating conditions [691]. The time interval from the onset to maximum blockade is slow, 4 (SD 6) min and the time to full recovery of T1, 15.6 (SD 0.9) min after injection [691]. The slow onset time limits the usefulness of this technique. Intralingual or submental routes have also been used in children, but data in neonates are lacking.

Pharmacokinetics

The dose of NMBDs at different ages depends on a complex interweaving of pharmacodynamic and pharmacokinetic factors. Age-related pharmacokinetics of d-tubocurarine in children is displayed in Table 3.4 [94]. The volume of distribution mirrors changes in ECF and can be predicted using either an allometric 3/4 power model or the surface area model, both of which approximate changes in the ECF with weight [499]. This occurs, because ECF is a major contributor to the volume of distribution at steady state (Vss). These volume changes are true for both depolarizing (succinylcholine) [692, 693] and nondepolarizing NMBDs [694].

The clearance of d-tubocurarine, standardized to an allometric or surface area model, is reduced in neonates and infants compared with older children and adults [94]. These age-related changes in clearance follow age-related maturation of glomerular filtration in the kidney [75], which is the elimination route of d-tubocurarine. Total plasma clearance of other nondepolarizing muscle relaxants (alcuronium,) that are cleared by renal and/or hepatic pathways (pancuronium, pipecuronium, rocuronium, and vecuronium) are all reduced in neonates [676, 678, 695–697]. In contrast, the clearances of atracurium and cisatracurium are independent of renal and hepatic pathways; rather, clearance depends on Hofmann elimination, ester hydrolysis, and other unspecified pathways [698]. Clearance of these drugs is greater in

Table 3.4 Age-related pharmacokinetics (SD) of d-tubocurarine (data taken from Fisher DM et al. *Anesthesiology* 1982; 57: 203–8) [94]

	Weight (kg)	CL (mL/min/kg)	CL Surface Area (mL/min/m [2])	CL Allometric 3/4 (mL/min/70 kg)		
(A) Total body clearance						
Neonate (1 d–2 mo)	3.5	3.7 (2.1)	56 (32)	122 (70)		
Infant (2 mo–1 y)	7	3.3 (0.4)	59 (7)	130 (15)		
Child (1–12 y)	22	4 (1.1)	110 (30)	210 (58)		
Adult (12–30 y)	60	3 (0.8)	115 (31)	202 (54)		
(B) Volume of distribution at steady state						
	Weight (kg)	Vdss (L/kg)	Vdss Surface Area (L/m [2])	Vdss Allometric (power 1) (L/70 kg)	Vdss Allometric (power 3/4) (L/70 kg)	
Neonate	3.5	0.74 (0.33)	11 (5)	52 (23)	25 (11)	
Infant	7	0.52 (0.22)	9 (4)	36 (15)	21 (9)	
Child	22	0.41 (0.12)	11 (3)	29 (8)	22 (6)	
Adult	60	0.3 (0.1)	12 (4)	21 (7)	20 (7)	
(C) Half-times						
	Chronological time (min)			Physiological time (min)		
	$T_{1/2}\alpha$	$T_{1/2}\beta$	$T_{1/2}$keo	$T_{1/2}\alpha$	$T_{1/2}\beta$	$T_{1/2}$keo
Neonate	4.1 (2.2)	174 (60)	6.3 (3.5)	8.7 (4.7)	368 (127)	13.3 (7.4)
Infant	7.0 (4)	130 (54)	7.5 (3.5)	12.9 (7.4)	240 (100)	13.9 (6.5)
Child	6.7 (2.4)	90 (23)	7.9 (2.7)	8.9 (3.2)	120 (31)	10.6 (3.6)
Adult	7.9 (4.1)	89 (18)	6.8 (1.9)	8.2 (4.3)	93 (19)	7.1 (2.0)

neonates when expressed on a per kilogram basis [699–701]. When clearance is standardized using allometric 3/4 power scaling, the clearances for atracurium and cisatracurium are similar across all age groups. The clearance of succinylcholine, expressed on a per kilogram basis, also decreases with increasing age [87, 88]. Succinylcholine is hydrolyzed by butyryl-cholinesterase. These observations are consistent with that observed for the clearance of remifentanil [476], which is also cleared by plasma esterases. These clearance pathways are mature at birth.

Conversion of d-tubocurarine half-times from chronological time to physiologic time is revealing. $T_{1/2}\alpha$ increases with age in chronological time, but in physiologic time, it is the same at all ages, as expected from a distribution phase standardized by allometry. $T_{1/2}\beta$ decreases with age in physiologic time, consistent with reduced clearance related to volume in the very young. The $T_{1/2}$keo is large in neonates and infants, reduced in children, and further reduced in adults. The cause for this change with age is unclear, but it may be related to an increased muscle bulk and concomitantly increased muscle perfusion in older children and adults.

Antagonism of Neuromuscular Blockade

Although edrophonium may establish a faster onset of effect, final recovery is invariably greater with neostigmine, which is why the latter is recommended for routine pediatric practice [702, 703]. The distribution volumes of neostigmine are similar in infants (2–10 months), children (1–6 years), and adults (Vss 0.5 L/kg), whereas the elimination half-life is less in the pediatric patients [704]. Clearance decreases as age increases (13.6, 11.1, 9.6 mL/min/kg in infants, children, and adults 29–48 years) [704] as we might expect from allometric scaling. The dose of neostigmine required to reverse d-tubocurare blockade was 30–40% less for infants and children than for adults (expressed as per kilogram) with a duration of effect of neostigmine similar in both pediatric and adult patients. Other studies have confirmed that a train-of-four (TOF) ratio recovers to 0.7 in less than ten minutes when a 90% neuromuscular blockade from pancuronium is antagonized with neostigmine 30–40 μg/kg in infants, children, or adults [703, 705–707].

Neonates have the more rapid times to full recovery after neostigmine antagonism [703, 708]. For example, reversal of an atracurium-induced 90% neuromuscular block in infants and children by neostigmine 50 μg/kg was fastest in the youngest age group [702]. The time to a TOF-ratio of 0.7 was 4 min in neonates and infants, 6 min in 2–10 years old children, and 8 min in adolescents. These observations are consistent with allometric models for size [46].

Sugammadex is a new drug that reverses the NMB effects of rocuronium and, to a lesser extent, vecuronium. It has a cylinder-like cyclodextrin structure that irreversibly encapsulates rocuronium into its cavity. An early sugammadex study in children suggests that sugammadex 2 mg/kg reverses a rocuronium-

induced moderate neuromuscular blockade in infants, children, and adolescents [709]. The average time to recover a TOF-ratio of 0.9 at the time of appearance of the second twitch response was 1.2, 1.1, and 1.2 min in children, adolescents, and adults, respectively. Sugammadex is cleared through the renal system and the elimination kinetics of rocuronium is prolonged in case of renal failure [710]. Although GFR is immature in neonates, this is unlikely to be of consequence here. Sugammadex has been used in patients with end-stage renal failure [711, 712] with similar reversal characteristics as those with normal renal function. Sugammadex has been associated with hypersensitivity and anaphylactic reactions in adults, although similar evidence has not been forthcoming in children except anecdotally [713, 714].

Adverse Effects

Succinylcholine is the most pilloried NMBD despite its importance for rapid sequence intubation [715–717]. Its molecular structure resembles that of two acetylcholine molecules joined by an ester linkage. Consequently, stimulation of cholinergic autonomic receptors can be associated with cardiac arrhythmias, increased salivation, and bronchial secretions. Muscle fasciculation is also associated with mild hyperkalemia (0.2 nmol/L), increased intragastric and intraocular pressure, masseter spasm, and skeletal muscle pains. Severe hyperkalemia may occur in patients with burns, upper and lower motor neuron lesions, trauma, and disuse atrophy. This may be associated with rhabdomyolysis and myoglobinemia in those patients suffering neuromuscular disorders. These disorders are not always diagnosable in neonates. Congenital myotonic dystrophy, for example, may present with mild respiratory dysfunction or feeding difficulty in the neonate. The response to succinylcholine in these neonates, however, remains dramatic with sustained muscle contraction [718]. Succinylcholine is a trigger for malignant hyperthermia, particularly in combination with inhalational anesthesia. Succinylcholine has a prolonged effect in children with butyryl-cholinesterase deficiency (plasma cholinesterase). This is an inherited disease due to the presence of one or more abnormal genes (atypical, fluoride-resistant, and silent genes) [657]. On the other hand, one genetic variant, the Cynthiana or Nietlich variant [719], represents an ultrarapid rate of degradation of succinylcholine [720].

The nondepolarizing NMBDs all have different adverse effects that are often used to therapeutic advantage. d-tubocurarine may produce hypotension and bronchospasm after large doses and a rapid administration. Pancuronium confers sympathomimetic effects as a result of blocking the reuptake of noradrenaline; the resultant tachycardia may augment cardiac output during induction for cardiac surgery in neonates. Doses greater than the ED_{95} of rocuronium have also proven popular for cardiac surgery to capitalize on its vagolytic activity that increases heart rate. Unfortunately, rocuronium also causes local pain when injected rapidly and may trigger anaphylaxis [721]. Atracurium can liberate histamine, precipitating bronchospasm and hypotension. These effects are attenuated with the isomer cis-atracurium.

Anticholinergic Drugs

These drugs block acetylcholine at the postganglionic cholinergic (parasympathetic) endings. They also block the direct vasodilator effect of acetylcholine on blood vessels (antimuscarinic) and in the CNS. They cause mydriasis and increase intraocular pressure, tachycardias, inhibit sweating, reduce salivation, decrease lower oesophageal sphincter tone, and have similar effects on tone in the digestive and urinary tracts. Atropine, scopolamine, and glycopyrrolate are the three commonly used anticholinergic drugs in anesthesia. Differences in clinical effects are not very prominent in healthy patients [722].

While these drugs are commonly administered with the anti-cholinesterases to reverse residual neuromuscular blockade, their routine use in neonatal anesthesia is declining [723]. The benefits of reduced secretions or prevention of bradycardia during otolaryngological surgery, eye surgery, and endoscopic procedures in children less than one year of age justify their use by some [724], although this continues to be debated [725]. They were used in the past to reduce salivation associated with ketamine, but ketamine use is also declining in neonates, while neuroapoptotic effects are investigated.

Atropine

Atropine is metabolized in the liver by N-demethylation followed by conjugation with glucuronic acid [726]; both processes are immature in the neonate. Half the drug is also eliminated by the kidneys. An old technique to diagnose atropine poisoning was to put a drop of the victim's urine into the eye of a cat and observe for mydriasis.

It is anticipated that clearance is reduced in the neonatal age range because of an immaturity of renal and hepatic function, but data remain elusive. Children, less than 2 years of age, have an increased volume of distribution at steady state (3.2 SD 1.5 vs. 1.3 SD 0.5 L/kg) compared with those older than 2 years [727] Clearance was similar in those aged less than 2 years (6.8 SD 5.3 mL/min/kg) and those older than 2 years (6.5 SD 1.6 mL/min/kg). The elimination half-life in healthy adults is 3 SD 0.9 h, whereas in term neonates, it is 4 fold greater [726]. There are no data from preterm neonates [727, 728].

Atropine 0.1 mg is widely reported to be the minimum intravenous dose in neonates and young infants. The provenance of this recommendation is a single study in which two infants and three children suffered neither bradycardia nor sequelae after small serial doses of atropine [729]. The risk from adhering to this minimum dose is a relative overdose of atropine in very low birth weight and extremely preterm infants. A dose of 5 μg/kg in infants (total <0.1 mg) demonstrated no adverse bradycardia or other adverse effects [730]. Systolic blood pressure did not change for any dose of atropine (5–40 μg/kg). Maximum heart rate change and minimum saliva flow occurred within 7–8 min after intravenous drug administration in adults, but neonatal data are lacking [731].

Scopolomine

Scopolamine is a tertiary amine with greater CNS effects than atropine, causing sedation and amnesia. Its moderate antiemetic activity [732] is of little use in neonates. The drug, combined with morphine, was a popular intramuscular premedication but is unsuitable in neonates. Routine intramuscular premedication has lost favor; intramuscular morphine-scopolamine causes hypercarbia and oxygen desaturation [733]. Scopolamine is considered a less effective agent to block cardiac vagal responses but confers a greater drying effect compared with atropine, although these differences in clinical effects are not very prominent in healthy patients [722]. A direct correlation between serum concentrations of scopolamine and changes in EEG signals in adults has been reported, but data in neonates are lacking [734].

Scopolamine has a distribution volume of 1.4 L/kg [735] in adults. Glucuronide conjugation, sulfate conjugation, and hydrolysis by the CYP3A family are involved in its clearance [734]. Both glucuronidation and the CYP3A enzyme systems are immature at birth and clearance is anticipated to be reduced. The pharmacokinetics of scopolamine is poorly understood [735].

Glycopyrrolate

Glycopyrrolate is a quaternary ammonium compound with poor CNS penetration. It has pronounced antisialogogue activity [736], although heart rate, demeanor, and facial flushing after intramuscular injection of atropine or glycopyrrolate were similar in 80 infants less than 1 year of age [737]. The drug remains popular for antagonizing the parasympathomimetic effects of neostigmine and is as effective as atropine for preventing the oculocardiac reflex [738].

Scopolamine is poorly absorbed from the GI tract (10–25%) [739]. Clearance in infants less than 1 year of age (n = 8) was 1.01 (range 0.32–1.85) L/kg/h and Vss 1.83 (range 0.70–3.87) L/kg), although there are no neonatal data. The renal system accounts for 85% of elimination [740], and clearance is anticipated to be reduced in neonates, because renal function is immature [75].

Adverse Effects

Poisoning signs and symptoms in adults can be described as "hot as a hare, blind as a bat, dry as a bone, red as a beet and mad as a hen." [741] These relate to the peripheral effects of dry mouth, blurred vision, and hot, dry skin; central effects contribute hyperpyrexia, restlessness, anxiety, excitement, hallucinations, delirium, and mania. Cerebral depression and death can occur in severe poisoning. The mydriatic effect on the eye when solanaceous plant (e.g., *Atropa belladonna*) extract is used topically has been employed to lure male suitors even though it causes the female to be somewhat uncertain of her beau's features.

The vagal response is greater in neonates than adults. The resulting tachycardia may be beneficial during anesthesia in neonates with their rate-dependent cardiac output. Propofol in combination with remifentanil can cause profound bradycardia during induction, as may repeat dosing of succinylcholine, laryngeal instrumentation, and surgical manipulation of the eye, testes, and hollow viscera. Prophylactic use of atropine may prove useful [742]. Hypoxaemia, however, is the commonest cause of bradycardia and this is managed with oxygen, not atropine.

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The Selection of Anesthesia Techniques for the Neonate

4

Nada Sabourdin, Nicolas Louvet, and Isabelle Constant

Part 1. General Principles and Aims of Anesthesia in the Neonate

To identify the optimal anesthetic technique for neonates, it is incumbent to articulate the goals of a safe and effective neonatal anesthesia.

- To allow the surgical procedure to be performed under the best possible conditions, while optimizing the physiological state and to provide analgesia sufficient to obtund physiological and neuroendocrine responses to the surgical stimulation. Special attention is needed to optimize oxygenation and ventilation, ensure thermal homeostasis, and glucose metabolism (see related chapters).
- To minimize unpleasant implicit memories.
- To minimize the risk of cerebral insults and damage whether hypoxic/ischemic, metabolic, or neurotoxic.

First Objective: To Provide Optimal Conditions for Surgery and Maintain Homeostasis.

Neonatal surgery is very precise and requires a totally immobile operative field. Any movement during surgery exposes the neonate to the risk of surgical and/or anesthetic complications. Neuromuscular blockade can ensure immobility, but it should be used with adequate analgesia. Disturbances in homeostasis can occur when the neonate is stressed from metabolic, hypothermic, hypovolemic, or nociceptive sources. Regulation of the metabolic balance, temperature monitoring, and intravenous fluid management are crucial endpoints for the safe conduct of anesthesia in the neonate.

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Prevention of nociceptive stress requires adequate analgesia, which may be a tricky balance, particularly if extubation is planned at the conclusion of the surgery.

The anatomical and physiological pathways of nociception are present and functional in utero, although central modulation may be primitive at that time. Optimal analgesia can be obtained by various techniques including inhalational agents, intravenous opioids, and/or regional anesthesia. The most common option is to provide a "balanced analgesia," combining inhalation agents, opioid and nonopioid analgesics, together with regional analgesia when appropriate. In the neonatal period, medullary reflexes are very robust: an adequate level of hypnosis and an adequate analgesia are required to ensure immobility at surgical incision. MAC values for inhaled anesthetic agents increase with decreasing age, but are less in neonates than in older infants, with the exception of sevoflurane (see Chap. 3). This may present challenges to maintaining circulatory homeostasis while delivering adequate anesthesia. The balance between cortical and subcortical processes in the neonate may differ from that in older children or adults with subcortical structures, at least at the level of the spinal cord, being less sensitive to sevoflurane-induced inhibition.

Hypnotics and analgesics (above their minimum dose necessary) decreases motor responses but may not be tolerated in some and may compromise the circulatory indices, return of spontaneous respiration and delay emergence. For these reasons, anesthesia in the neonate may be complemented by neuromuscular-blocking agents. In the past, they might have been used *instead of* adequate analgesia, but today, they are combined with adequate analgesic and hypnotic drugs to ensure immobility during surgery. Given the immaturity in clearance and renal function in the neonate together with the interindividual variability in pharmacodynamic responses, every drug should be titrated in the neonate to achieve the desired endpoint.

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Second Objective: To Avoid the Storage of Unpleasant Implicit Memories

Special attention should be directed in the perioperative period, before and after anesthesia to avoid the perception, integration, and memorization of stressful experiences commonly encountered at this time: fear, cold, hunger, loud noise, bright lights, inadequate handling, uncomfortable position, unfamiliar voices, faces or smells, and, most importantly, pain. This will not only limit the temporary unpleasantness of the procedure but might also preclude long-term behavioral and/or emotional disturbances.

The development of memory processes in very early life is poorly understood [1]. Freud described the inability of adults to recall birth and those events early in life in the consciousness as "infantile amnesia." Although episodic events in the early postnatal years cannot be recalled later in life as conscious recollection (explicit memory), that does not mean that the events did not impact our developing subconscience through implicit memory [1, 2]. Memories of episodic events involving the "who, what, when and where" or "wwww" memories are referred to as hippocampal memory, which depend on a collaborative integration of memory traces or engrams with other regions of the brain including the medial temporal lobe, amygdala, and cortical regions to consolidate long-term memory. After studying the fading of episodic memory in rodents, studies undertaken in humans indicated that the 3 year old can retain episodic experiences in the short term but that those memories fade rapidly and are forgotten in the long term. In most, recall of episodic experiences before the age of 10 years is sparse and incomplete [3]. Numerous theories have been proposed to explain the long-term inability to recall episodic memory in infancy including the lack of linguistic abilities, but after similar memory loss was discovered in young animals, the theories pointed to developmental aspects of specific regions of the brain. In fact, our inability to recall episodic events from infancy may in part be attributed to immaturity of the dentate gyrus of the hippocampus, amygdala, and prefrontal cortex. The former matures by 3–5 years age, which corresponds to the age at which "infantile amnesia" ceases to be a consideration and the latter by adolescence and early adulthood. Further evidence suggests that our inability to recall those early events may stem more from a process retrieval problem rather than a decay in or loss of the actual memory [3]. At the same time, when the neonate experiences smells, voices, vision, and music, each experience contributes to the functional maturation and learning system of the hippocampus. Although explicit memory only achieves maturity after several postnatal years, implicit memory is probably fully functional from birth and possibly in utero as well (Fig. 4.1) [4–8].

Paradoxically, one may question how psychopathogical external factors (such as neglect or pain) that are experienced in early life can impact behavior later in life (e.g., personality disorder or exaggerated response to a noxious stimulus) if the early memories cannot be retrieved? [9–11] Implicit memory is memory that has been retained not in the consciousness but in the subconscious. Even though the events are not retrievable, these events help develop and adapt our behaviors and responses to subsequent situations. Implicit

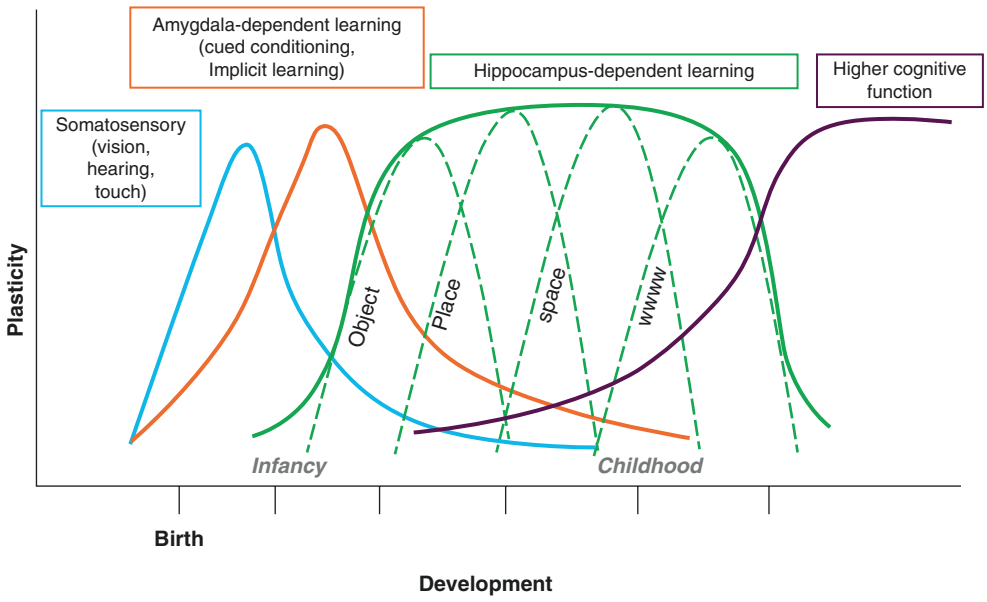

Fig. 4.1 Critical windows of sensitivity for brain functions. Solid curves indicate the normal expression of the critical period within each brain region in infancy and childhood. Hippocampal-dependent learning includes sequential waves of sensitivity, which enable acquisition of increasingly complex functions including object, place, space and wwww (who, what, when and where). Reproduced with permission, Ref. [2]

memory is primarily associated with different areas of the brain unlike explicit memory, specifically the striatum, cerebellum, and amygdala, areas that are present in nonhuman primates and the first to mature [12]. Implicit memory has been detected in fetuses in studies in which they were provoked with a noxious stimulus. Implicit memory develops throughout postnatal life after stabilizing after 8 months of age, integrating experiences and responses in life into the subconscious. Testing implicit memory in early infancy, however, has proved to be challenging although research has demonstrated that the responsiveness to a stimulus (often noxious) is more rapid and severe after a prior exposure [13]. Although the infant may not have had explicit recall of the prior event, the vigor and extent of their responses to the subsequent stimuli were greater than their responses without a prior exposure or a painless exposure [14]. These experiences, which may have occurred in the preverbal period or under anesthesia, nonetheless led to exaggerated or more extreme responses when subsequently challenged. Hence, it behooves us to minimize nociceptive stimuli in the neonate and infant at all ages by providing adequate analgesia and anesthesia to preclude the development of implicit memory.

Third Objective: To Ensure That the Techniques Employed Minimize the Risk of Cerebral Damage (Hypoxic/Ischemic, metabolic, or neurotoxic)

The brain in the neonate is fragile and can be harmed in many ways during anesthesia. Any severe homeostatic disturbance might lead to brain injury. Most commonly, inadequate cerebral oxygen delivery is the underlying cause. This may result from ventilatory or circulatory causes, or a combination of the two. Less commonly, metabolic (e.g., hypoglycemia, hypothermia) or neurotoxic causes may be implicated.

Cerebral Hypoxia/Ischaemia

Hypoxia occurs when cerebral cells do not receive sufficient oxygen to meet their basic metabolic needs. This can occur under three conditions: low oxygen content (as measured by the saturation), low delivery (cerebral blood flow), or both is present. Low arterial oxygen saturation is most frequently secondary to loss of the airway (e.g., failed intubation or inadvertent extubation) or impaired ventilation/perfusion mismatch that arises from primary pulmonary disorders (e.g., chronic bronchopulmonary dysplasia) or intracardiac shunts. It is vitally important to monitor oxygenation and ventilation meticulously during anesthesia (See Chap. 7).

Cerebral blood flow is most commonly insufficient due to systemic hypotension. In nonanesthetized term neonates, the normal MAP increases from approximately 52–61 mmHg during the first month of life [15], SBP from approximately 62 to more than 80 mmHg [16]. The slope of the blood pressure increase is maximum during the first week of life. Blood pressure in preterm neonates tends to exceed that in term neonates of similar postmenstrual age [17]. Despite our knowledge of these data in awake neonates, there has been a lack of knowledge regarding the normal range of blood pressure in anesthetized neonates. This was due in part to a lack of attention to the correct way to measure blood pressure in the neonate (cuff size, position, and device) to obtain precise results. Attention was drawn to this issue when a case series described postoperative encephalopathy in six young infants (<48 weeks postmenstrual age) who developed early postoperative seizures [18]. One patient died, another had severe neurodevelopmental sequelae. Although these postoperative complications had no definitive explanation, the six cases shared a common feature: the intraoperative mean arterial pressure was relatively low. In 2016, a retrospective observational study including more than 100,000 ASA 1-2 children, 2122 of whom were less than 2 months postnatal age, provided the first pediatric descriptive data for normal intraoperative blood pressure [19]. This report, however, did not analyze the relationship among blood pressure levels, organ perfusion, and postoperative outcomes.

The lower limit of intraoperative blood pressure below which brain damage may occur in neonates remains uncertain. Cerebral perfusion pressure is defined by the difference between mean arterial pressure (MAP) and intracranial pressure (or central venous pressure). If intracranial pressure remains constant, cerebral perfusion pressure depends directly on the MAP. Cerebral autoregulation delivers a constant cerebral blood flow within the normal range of MAP by increasing or decreasing the caliber of the cerebral vessels inversely to the change in MAP. When MAP decreases below the lower limit of autoregulation, cerebral vasodilation is maximized and cerebral blood flow becomes pressure dependent, for example, it depends directly on the MAP. Below a critical level of MAP, cerebral blood flow becomes insufficient to supply sufficient oxygen to the brain cells and cellular hypoxia ensures. In anesthetized neonates, the autoregulation plateau is narrower than in adults, but its limits have not been definitely established. Moreover, in recently asphyxiated neonates, the plateau may be narrower or possibly nonexistent. Using cerebral blood flow velocity and near infrared spectroscopy (NIRS), studies performed at 1 MAC sevoflurane showed that the lower limit of autoregulation in infants less than six months of age was an MAP of

45 mmHg. Cerebral oxygenation was impaired at an MAP of under 35 mmHg of MAP in these infants [20], although there was an element of interindividual variability in the measurements. No specific recommendations were made for the minimum MAP in neonates, although these findings provided a solid foundation on which to base the hemodynamic management of neonates under anesthesia. Thus, to limit the risk of brain damage, the minimum MAP should exceed 35 mmHg at all times during neonatal anesthesia.

Insufficient cerebral blood flow can also be the consequence of excessive vasoconstriction [21, 22], the result of hyperventilation and hypocapnia. As carbon dioxide vasoreactivity in children is particularly marked, avoiding hypocapnia is of paramount importance during anesthesia.

Metabolic, Neurotoxic, and Other Potential Causes of Cerebral Damage.

The neonate, in particular, the asphyxiated and the preterm neonate, is prone to hypoglycemia. Consequently, an infusion of glucose should be delivered perioperatively while the blood glucose concentrations are monitored. Caution should be exercised to avoid the possibility of both hypoglycemia and hyperglycemia. The latter state may increase the danger of cerebral damage and also cause fluid and electrolyte disturbance.

The neurotoxic potential of anesthesia drugs is discussed in detail in Chap. 18.

Part 2. Techniques of Anesthesia

Spinal Anesthesia

In the 1980s, spinal anesthesia became popularized as an alternative to general anesthesia in preterm and ex-preterm infants as it did not increase the risk of postoperative apnea [23, 24]. In 1998, a landmark study reported that the frequency of postoperative apneas in infants who were born prematurely and who underwent inguinal hernia repair under spinal anesthesia was less than in those who underwent general anesthesia using thiopental and halothane [25]. For the infant born prematurely, an analysis of four trials determined that the risk of apnea decreased steadily between birth and 60 weeks post-conceptional age (PCA), at which point it was less than 1% [26]. At 45 weeks PCA, this risk was approximately of 5% [26]. Anemia (hematocrit <30%) [26–28] hypothermia [29] premature neonates with a pre-existing impaired respiratory function than spinal anesthesia [30]. Spinal anesthesia has increasingly become the preferred technique for brief surgical procedures in the inguinal and lower abdominal areas in neonates born prematurely. This practice has remained unchanged over the past three decades despite the introduction of newer, less soluble inhalational anesthetics [31].

In 2015, a Cochrane review on "regional (spinal, epidural, caudal) versus general anesthesia in preterm infants undergoing inguinal herniorrhaphy in early infancy" [32] concluded that there is "moderate-quality evidence to suggest that the administration of spinal in preference to general anesthesia without pre- or intraoperative sedative administration may reduce the risk of postoperative apnea by up to 47% in preterm infants undergoing inguinal herniorrhaphy…". For every 4 infants treated with spinal anesthesia, one may be prevented from having an episode of postoperative apnea. Finally, the beneficial effects of spinal versus general anesthesia in this context were confirmed in a recent meta-analysis based on 6 studies, including a total of 512 patients born prematurely and undergoing inguinal hernia repair [33]. The conclusion published was that compared with general anesthesia, spinal anesthesia reduced the risk for any postoperative apnea, bradycardia, and the need for mechanical ventilation in this population.

One of the studies included in this last meta-analysis was the General Anesthesia compared to Spinal anesthesia trial (GAS) [34]. This study was the largest international randomized controlled trial ever published on the issue of postoperative apnea in infants undergoing inguinal herniorrhaphy, although its primary aim was to assess neurodevelopmental outcome after anesthesia in early infancy. The GAS study included infants aged 60 weeks or younger postmenstrual age, randomly allocated to sevoflurane-based general or awake regional anesthesia. The main result of the secondary outcome of that study was that the risk of apnea beyond 12 h after surgery allocation was unaffected by which anesthetic technique was used, regional or general anesthesia. However, regional anesthesia did reduce the incidence of early apnea (within 30 min of the end of surgery), as well as its severity: all children (0.8%) who had an apneic episode requiring positive pressure ventilation or cardio-pulmonary resuscitation had received general anesthesia. Also, postoperative desaturation was less frequent with regional anesthesia. The strongest risk factor for postoperative apnea was preterm birth: 24 of the 25 patients who had postoperative apnea were born prematurely, the last one was born at 37 weeks and one day. Thus, in 2015, using modern agents and techniques of anesthesia, the incidence of postoperative apnea in preterm infants was 6.1% compared with 0.3% in term infants. Because of the significant risk of postoperative apnea, infants aged less than 60 weeks PCA who were born prematurely require 12 h of apnea-free respiratory monitoring after surgery, irrespective of the anesthetic provided. Some have suggested that those infants who were born premature but are now greater than 46 weeks PCA without anemia or comorbidities may be discharged earlier, that is, after

six hours of monitoring [35]. This recommendation requires prospective evaluation.

In addition to its benefit on the incidence of postoperative apnea and desaturation, spinal anesthesia has several advantages in terms of safety and comfort. First, the patient breathes spontaneously, avoiding all possible complications related to airway devices. Second, as opposed to older children, spinal anesthesia does not induce clinically significant hemodynamic disturbances in the neonate. In particular, arterial blood pressure remains stable [36, 37]. When no general anesthetics are administered, blood pressure levels do not significantly decrease intraoperatively [38, 39]. In the GAS study, the mean minimum systolic blood pressure in infants who received spinal anesthesia was greater than that in infants who received general anesthesia (70.7 versus 54.8 mmHg) and the infants were less likely to need an intervention for hypotension during the procedure. Finally, infants who have received spinal anesthesia were very calm and peaceful during the surgery and some actually fell asleep. Interestingly, the BIS has been recorded in unpremedicated infants who were born premature undergoing surgery with spinal anesthesia. The BIS decreased during the first 25 min after the spinal, to reach a nadir of 60, that remained unchanged for the next 20 min, and finally returned to 100 during the final 20 min [40]. This decrease in the BIS measurements during spinal anesthesia has been attributed to an attenuation of the ascending sensory input to the brain, permitting sleep.

Does the use of spinal analgesia remove the possibility of anesthesia-related cerebral toxicity? Based on clinical observations of transient or persistent neurological symptoms after spinal anesthesia in adults [41], a direct cytotoxicity of local anesthetics has been suspected and investigated. Neurotoxicity was first characterized in animal studies [42] and then in in vitro human neuronal cells models [43]. The mechanisms are still unclear and may be multifactorial. However, all local anesthetics, and particularly bupivacaine and lidocaine, have triggered dose-dependent neuronal cell dysfunction, death, or apoptosis, at in vitro concentrations similar to or less than clinical concentrations observed in the CSF after standard spinal anesthesia. Evidence suggested that spinal anesthesia does not trigger apoptosis in newborn rodents that received spinal anesthesia on postnatal day 3, 7, 14, and 21 [44], including on day 3 at the peak of rapid synaptogenesis in the dorsal horn of the spinal cord [45, 46]. Although a certain degree of local anesthetics toxicity might exist in the neonatal period, data from in vitro and animal studies are so far rather reassuring.

Complications from spinal anesthesia as documented from several large studies are rare [47–50]. In neonates, the rate of complications may be as low as 0.29% [45]. The theoretical risk of septic or aseptic meningitis is very small and has only been reported in two children. In both instances, the role of dural puncture remained uncertain [50, 51]. A high blockade requiring ventilatory assistance (0.67% in one series) or intubation (0.33%) [52] is also unlikely, provided the correct dose is administered, and the infant remains strictly horizontal. Neuraxial hematoma has not been reported in a child, although it has been described in an infant undergoing diagnostic lumbar puncture, who had undiagnosed hemophilia A [53]. The utility of tests of coagulation indices in children undergoing lumbar punctures under spinal anesthesia remains contentious [54] and is not standard practice.

The main concern regarding spinal anesthesia in the neonate is its failure rate. The reported failure rate of spinal anesthesia is between 3% and 20%, depending on the experience of the anesthesiologist with spinal blocks [32, 34, 47, 49, 52, 55–57].

Regarding the duration of spinal anesthesia, there is interindividual variability, and the duration of analgesia and motor block varies according to the type and dose of the local anesthetic chosen. In most cases, the duration of the block is a maximum of 90 min [47], which limits the duration of the surgical procedure under spinal anesthesia. Spinal anesthesia has been used for various infra-umbilical procedures, but also occasionally for pyloromyotomy [38, 58, 59] and at least once for duodenal atresia repair [60].

In conclusion, spinal anesthesia offers numerous advantages over general anesthesia and is associated with few complications. Although useful in the infant who was born premature and remains less than 60 weeks' PCA, it may be considered in the neonate undergoing any mid and lower abdominal surgery of less than 60 min in duration. Recent concerns about potential local anesthetic neurotoxicity have been articulated in the literature. However, the evidence arises primarily from animal and experimental studies, and the clinical relevance to humans is yet to be established. When the location and duration of surgery make it appropriate, spinal anesthesia may be the optimal option for the neonate.

With the substantial failure rate from spinal anesthesia as mentioned above, as well as its limited duration of action (<90 min) and the infrequency of performing spinal blocks in young infants, clinicians have turned to continuous caudal anesthesia as an alternate regional anesthetic technique. Here, the infant is curled in the lateral decubitus position, the caudal space is prepared aseptically and a short epidural catheter (18 or 20 gauge) is introduced through an intravenous catheter or epidural needle. The catheter is fixed in place with sterile dressing to use throughout the surgery. Initially, lidocaine 1.5% with epinephrine (diluted to 0.75–1% with sterile saline) was administered in a dose of 7 mg/kg lidocaine for the procedure without supplemental sedation. However, as repeated doses of lidocaine could not be administered, some have turned to 3% 2-Chloroprocaine in 10–30 mg/kg boluses through the epidural catheter: this may be administered until the desired height of the block is achieved fol-

lowed by 15–30 mg/kg/h.(see Chap. 16) [61] Some have diluted the 3% 2-Chloroprocaine to 1.5% to increase the volume spread of the epidural solution [62]. Since the action of chloroprocaine is terminated by pseudocholinesterase, there is no fear of accumulating doses of chloroprocaine that could lead to an overdose or toxic sequelae. Oral sucrose via the pacifier and music may be added to soothe the child during the surgery. This technique has a high success rate, provides excellent quality of anesthesia, and avoids any limit on the duration of surgery.

Induction of General Anesthesia for Elective Surgery

In the past, anesthesiologists faced hemodynamic and respiratory consequences of anesthetic agents in children. Halothane, in particular, caused myocardial depression, bradycardia, and arrhythmias.

Hypnotics, opioids, and muscle relaxants in excessive dose could produce severe hypotension, tachycardia, bradycardia, dysrhythmia, chest rigidity, or respiratory depression. These could lead to fatal hemodynamic consequences or respiratory failure. To lessen the risk of such adverse events in neonates, practitioners administered the smallest possible doses of these drugs and limit the number of different drugs administered. In addition, many older drugs had prolonged durations of action or diverse dose-dependent side effects that prompted a polypharmacy approach to minimize these effects.

With the introduction of receptor-specific and better-tolerated anesthetics, induction of general anesthesia for elective surgery even in neonate is infrequently a problem. As cardiopulmonary morbidity has substantively decreased, latent fears have emerged about potential deleterious effects of anesthetics on neurologic development. Currently, these latter fears should not deter the clinician from administering appropriate anesthesia care.

Inhalational Induction

An inhalational induction is a suitable technique to induce anesthesia in the neonate undergoing elective surgery. In this age group, induction is rapid, smooth, technically easy to perform, and pain free. One of its main advantages is that it does not require that IV access be established while the infant is awake, a procedure that can be particularly difficult, prolonged, painful, and stressful for the struggling infant as well as for the anesthesiologist. Sevoflurane is the inhalational agent of choice for induction of anesthesia in infants. Unlike halothane, sevoflurane has an excellent cardiovascular profile, high concentrations of sevoflurane can be administered without leading to excessive circulatory depression. However, theoretical concerns have been raised regarding its potential to trigger epileptiform EEG activity [63], which might be observed during deep anesthesia, preceding the appearance of burst suppression. Epileptiform EEG activity occurs more frequently in the presence of both large concentrations of sevoflurane and hyperventilation [64, 65]. Major epileptoid signs were reported in 50% of children anesthetized with 1.5 MAC of sevoflurane in one study [66]. Evidence has shown that opioids and nitrous oxide decrease the incidence of epileptiform EEG activity [66]. However, epileptiform EEG patterns only weakly portend seizures. To date, there has been a dearth of EEG studies in neonates with only a single case of tonic clonic activity reported [67]. Since that single report, no further cases or reports of seizures in neonates and infants have been reported, nor have any restrictions been placed on the concentration of sevoflurane that may be administered to neonates and infants.

Tracheal intubation can be performed with sevoflurane alone in most infants and children undergoing elective surgery [68]. The main factor associated with success is to provide sufficient time from the beginning of the inhalational induction until an adequate depth of anesthesia has been achieved, one that often occurs after loss of spontaneous ventilation [69]. Both positive end-expiratory pressure (10 cmH_2O) and assisted ventilation speed the onset of a deep level of anesthesia [70]. Alternately, the time to tracheal intubation may be abbreviated by supplementing the inhalational induction with IV drugs such as propofol, opioids, and/or muscle relaxants [71]. These strategies have been studied in children and may be extended to neonates, although evidence in neonates remains lacking. In neonates, the time to induce anesthesia is rapid; however, with an MAC of 3.2% sevoflurane, the maximum MAC multiple that can be achieved within the first minute or two of anesthesia is only 1.2 (unlike halothane, which can achieve an MAC multiple of 2.5 within the same time) (see Chap. 3). Hence, to speed the induction of deep anesthesia, an IV dose of 1–2 mg/kg propofol may be administered [70, 71].

Use of Opioid Drugs to Facilitate Anesthesia Induction

The analgesic properties and adverse events of all opioids are dose dependent. But each opioid differs in its potency, onset of action, and duration of action.

Fentanyl (1–5 μg/kg) is one of the most frequently used analgesics for tracheal intubation in the NICU [72, 73]. This synthetic opioid has an analgesic potency 50–100 times that of morphine. It is quite lipid soluble and highly bound to plasma proteins. Its onset of clinical activity is approximately 1 min, with a duration of effect after a single IV dose of 30–45 min. Fentanyl's large hepatic extraction ratio implies that its termination of the action depends on both liver blood flow and CYP450 3A4/7 activity [74]. When hepatic blood flow is attenuated, as in several neonatal abdominal patholo-

gies with increased intra-abdominal pressure, the elimination rate may be dramatically reduced (approaching zero), with a correspondingly longer half-life [75, 76].

Fentanyl should be injected slowly IV, since it is associated with thoracic rigidity when injected rapidly. It provides excellent conditions for rapid intubation and with few hemodynamic adverse events when it is combined with atropine and a neuromuscular blockade [77–79]. Whether administered in bolus doses or as a continuous infusion, fentanyl maintains excellent hemodynamic stability [80].

Sufentanil is a synthetic opioid that is ten times more potent than fentanyl. It is highly lipid soluble and strongly bound to alpha-1-acid glycoprotein. In the neonate, the elimination half-life of sufentanil is increased. This is attributable to an increased volume of distribution and diminished clearance [81, 82]. It has an excellent hemodynamic tolerance, even at large doses [83]. Sufentanil can attenuate the cardiovascular response to intubation. Studies performed on a neonatal population are lacking, but some data on children 2–9 years of age, 0.3 μg/kg sufentanil combined with 2.5 mg/kg of propofol, and vecuronium, effectively blunted the cardiovascular responses to tracheal intubation [84]. The ED_{50} for sufentanil for excellent intubating conditions decreased as the expired fraction of sevoflurane increased in children [85]. For example, at 3% of sevoflurane, the ED_{50} was 0.32 mcg/kg sufentanil. However, considering the significant pharmacokinetic changes that occur during the first month of life, the extrapolation of these results to neonates should be viewed cautiously.

Although fentanyl and sufentanil remain the most frequent opioids administered to neonates before laryngoscopy and tracheal intubation, even shorter-acting opioids such as alfentanil and remifentanil have been evaluated.

Alfentanil is a synthetic opioid, derived from fentanyl. It is 5–10 times less potent than fentanyl and has a shorter onset and duration of action, mainly because of its reduced volume of distribution. Alfentanil is strongly bound to albumin but also to the plasma alpha-1 acid glycoprotein, a molecule present at reduced concentrations in the plasma of neonates compared with older children or adults [86]. Thus, like sufentanil, its free fraction is increased. The metabolism of alfentanil is mainly via hepatic enzymes, using metabolic pathways that are still immature at birth. In neonates, the elimination half-life is tenfold greater than in infants and children [87], attributable primarily to its decreased clearance [88]. In neonates, a bolus of 9–15 mcg/kg of alfentanil facilitates tracheal intubation and decreases the stress response to that procedure. However, alfentanil may induce a greater incidence of muscle rigidity compared to other opioids [89]; this adverse effect together with its prolonged elimination half-life limits the use of alfentanil in neonates.

Remifentanil is the most recent synthetic opioid to become commercially available. In contrast to other opioids, remifentanil is metabolized by nonspecific plasma and tissue esterases, with activities at birth similar to those in adults. Thus, the elimination of remifentanil is rapid and independent of hepatic and renal functions. The elimination half-life is very brief irrespective of the dose; its context-sensitive half-life is also independent of the age of the child, dose, and duration of infusion, approximately 3–5 min. Side effects associated with bolus doses of IV remifentanil, like other opioids, may be problematic: bradycardia, chest wall rigidity, respiratory depression, nausea and vomiting, and hyperalgesia may occur [77, 90, 91]. Remifentanil is 26–65-fold more potent than fentanyl, primarily binding to μ opioid receptors and secondarily to κ and σ receptors. There is no defined dosing in neonates. IV doses range from 1 to 5 mcg/kg for boluses and from 0.025 to 5 mcg/kg/min for infusions, depending on concurrent medications [91]. In neonates, a single bolus of 3 mcg/kg IV remifentanil for nonurgent intubation yielded less favorable intubating conditions than a combination of fentanyl and succinylcholine [92]. Remifentanil boluses have also been evaluated as adjuvants to propofol during intravenous induction of anesthesia in infants and children [93]. Although neonates have not been studied as a group distinct from infants, the ED_{50} and ED_{95} for remifentanil after propofol 5 mg/kg in neonates and infants <3 months of age to provide excellent intubating conditions were 3.1 and 5.0 mcg/kg [94]. A continuous infusion of remifentanil has also been recommended to complement sevoflurane during induction of anesthesia although studies in neonates are lacking. The principle of providing opioid analgesia before intubation seems reasonable, but the risk-benefit ratio in neonates is unknown. Nonetheless, it is important to administer sufficient doses of hypnotics, like sevoflurane or propofol, to attenuate the nociceptive and reflex responses to laryngoscopy at a cortical and even subcortical level.

Intravenous Induction

An intravenous induction of anesthesia is a common induction technique in neonates globally, since most neonatal surgery occurs in the peripartum period, is associated with a full stomach, and requires an RSI. These neonates arrive in the operating room from the NICU with an IV (or PICC line) in place. Thiopental (where it is available) or propofol is commonly used for induction of anesthesia.

Tracheal intubation can be performed effectively after IV propofol alone, but cannot be after thiopental or other IV hypnotic agents [95]. This property of propofol may be attributed to its ability to profoundly depress the laryngeal reflexes and relax the oropharyngeal muscles [96]. When compared with a combination of morphine, atropine, and succinylcholine, propofol 2.5 mg/kg led to a more rapid, successful intubation, less desaturation episodes, and a more rapid recovery time in 63 premature neonates undergoing nonurgent procedures [97]. However, it should be noted that

most anesthesiologists would use a larger dose of propofol if it were the only induction agent. The times to intubation were 120 versus 260 s for propofol versus the three drug regimen, times that far exceed those acceptable to anesthesiologists, and all neonates were intubated nasally. Finally, the intubations were performed by trainees, not attending faculty, again raising doubts about the external validity of the data. Similar criticisms hold true for much of the evidence emerging from the neonatology literature [98]. When inducing anesthesia with propofol, the clinician should gently hold the limb where the IV is located, in order to prevent brisk withdrawal movements that might result in loss of the line before all the drugs are injected. The IV site should also be visible at least until all the drugs have been infused. Accidental disconnections can lead to underdosage and airway or hemodynamic reactivity during laryngoscopy. The injection may be done slowly, titrating the optimal dose of hypnotic drugs to the clinical state of the neonate. Pain during injection of propofol is an issue in neonates, even if local anesthetics are added to the propofol. However, it may be attenuated by the prior injection of an opioid (see Anesthetics for RSI, below).

Dexmedetomidine is an IV sedative agent that has interesting potential in neonatal anesthesia. This α2-adrenoceptor agonist has sedative, anxiolytic, sympatholytic, and analgesic-sparing effects, associated with minimal depression of respiratory function. Dexmedetomidine is increasingly used off-label in infants and children with cardiac diseases, in anesthesia and intensive care [99]. Its pharmacokinetic and pharmacodynamic profile is still under investigation (see Chap. 3). Dexmedetomidine and general anesthesia have been compared in preterm and full-term infants <3 months of age for the perioperative outcomes after open inguinal hernia [100]. Both groups received a caudal block during surgery. Dexmedetomidine was given as a loading dose, 2 μg/kg over 10 min, followed by a variable infusion between 0.2 and 1 μg/kg/h as needed. Perioperative outcomes were similar the infants who received dexmedetomidine had lower heart rates and higher mean arterial blood pressures. Fewer infants who received dexmedetomidine required tracheal intubation and NICU admission than general anesthesia. Dexmedetomidine has also been used as a postoperative adjunct to opioids after surgery in neonates in the NICU [101]. An infusion of 0.36 μg/kg/h significantly reduced the use of opioids postoperatively in neonates after surgery, a benefit that was associated with a two-fold greater frequency of self-bradycardia compared to the opioid-alone group.

Other Issues During Anesthetic Induction

Muscle Relaxants for Tracheal Intubation

All NMBDs improve the conditions for tracheal intubation in neonates. However, for elective surgery, NMBDs are often unnecessary to achieve a quick and stress-free tracheal intubation, as most opt for hypnotics and opioids instead [102]. The latter drugs suppress consciousness, blunt the hemodynamic response to intubation, and, in sufficient doses, prevent movement. However, to limit hypotension after an intravenous induction, particularly in neonates from the NICU, a bolus of balanced salt solution (10 mL/kg) should be given before induction of anesthesia. It should also be noted that despite preoxygenation (see strategies below), neonates and in particular small neonates (<2 kg) may present challenges to ventilate and oxygenate by facemask should tracheal intubation prove to be challenging. In such cases, paralysis with succinylcholine or a nondepolarizing muscle relaxant may facilitate ventilation while alternate intubation strategies are prepared. Succinylcholine is seldom used in pediatric anesthesia any longer, not because it causes anaphylaxis (a rare complication), but primarily because it caused hyperkalemia in children with undiagnosed myopathies or neurological disorders (eg., undiagnosed Wernig Hoffman) that was misdiagnosed as malignant hyperthermia and treated with dantrolene in several cases [103, 104]. Correct treatment with intravenous calcium chloride or gluconate was delayed or omitted, which led to adverse outcomes and a proscription of succinylcholine use in children. With succinylcholine proscribed, the NDMAs became the standard in pediatric anesthesia with the benylisoquinolones and steroidal compounds (e.g., rocuronium) the most commonly used. Reports of anaphylaxis to relaxants highlighted succinylcholine, benzylisoquinolones (atracurium, mivacurium) and rocuronium as the primary putative agents [105]. Interestingly, the frequency of anaphylaxis to rocuronium in children in Europe far exceeded that reported in North America. Some suggested that anaphylaxis after the first exposure to rocuronium was due to cross-reactivity with epitopes (e.g., pholcodine) in specific products used in Europe [106]. As the use of these epitopes waned, so too has anaphylaxis to rocuronium. In instances where the neonate has been paralyzed with ≥1 mg/kg rocuronium and in whom tracheal intubation failed and ventilation proved difficult, reversal with 16 mg/kg immediately after rocuronium can restore spontaneous ventilation in this life-saving situation [107, 108]. Anaphylaxis to sugammadex has also been reported, although such events are rare in neonates and infants [109]. In general, anaphylactoid and allergic reactions as well as anaphylaxis are extraordinarily rare in neonates [110, 111].

Many jurisdictions have recommended that succinylcholine only be used for rapid sequence inductions and in emergencies (e.g., laryngospasm) because of its potential side effects. For the remainder of circumstances, a nondepolarizing agent can be used. In part, the proscription of succinylcholine can be traced back to some individuals misdiagnosing hyperkalemia after succinylcholine for malignant hyperthermia and failing to resuscitate the child with

calcium in a timely manner. In its stead, dantrolene was given. This delayed the appropriate treatment and resulted in unfavorable outcomes. Nonetheless, many younger anesthesiologists are unaware of the history behind the proscription of succinylcholine and have been trained to avoid succinylcholine except in emergent situations. This is most unfortunate as succinylcholine will be used in emergencies without appreciating the need for pretreatment with atropine to avoid bradycardia/asystole or the fact that the dose in neonates and infants is 2 mg/kg IV, twice that in adults.

In an effort to understand the role of sugammadex to reverse rocuronium, investigators analyzed the economics and quality of care of high-dose sugammadex to reverse high-dose rocuronium for RSI. They noted that compared with placebo, infants are more sensitive to NMBDs than older children: fewer than 50% of the receptors have to be occupied to achieve intubating conditions in young infants compared with 90% of the receptors in adults [112]. Hence, neonates require smaller doses of nondepolarizing relaxants to achieve a targeted effect, but the duration of paralysis will be markedly prolonged compared with that in children and adults [113]. Increasing the amount of injected NMBD speeds the time to peak effect, dramatically prolongs the duration of action of the NMBD [114].

The advantage of rocuronium is its rapid onset of action: 0.6 mg/kg induced good intubation conditions in 60 s in older children anesthetized with propofol [115]. However, the duration of action of rocuronium in neonates is prolonged and unpredictable [116]. In contrast, the onset times to profound neuromuscular block with mivacurium and atracurium (2–3 min) are greater than those for other muscle relaxants but their duration of action is brief. Mivacurium 200 μg/kg IV provides good intubating conditions after 90 s in children [117]. The addition of fentanyl decreased the number of attempts and also the frequency of desaturation during tracheal intubation in premature and full-term neonates [79, 118]. Intubating conditions were scored as excellent with muscle relaxation occurring within 94 s although the time to return of spontaneous movements was 15 min. However, a hypnotic drug was not included in this regimen. To date, the intubating conditions after mivacurium-fentanyl have not been compared to a hypnotic-fentanyl combination in neonates.

Mivacurium is degraded spontaneously by pseudocholinesterase, leaving no active metabolites. Similarly, atracurium is degraded spontaneously but by Hoffman degradation, a process that depends on pH and temperature [119]. In patients with plasma pseudocholinesterase deficiency (estimated frequency 1:2000), mivacurium may cause prolonged neuromuscular blockade. In neonates, the activity of these esterases is less than in older patients, approximately 50% of the adult normal rate. The maturation profile of this enzyme remains unclear: there may be a rapid increase in the pseudocholinesterase level in the first month of life and then a slower increase toward adult values [120]. In a neonatal case report of prolonged neuromuscular blockade after an injection of 0.2 mg/kg of mivacurium, plasma levels of cholinesterases were conclusive, and the diagnosis could only be confirmed by molecular investigation [121].

Cisatracurium is one of the ten stereoisomers that comprise the muscle relaxant, atracurium [119]. Cisatracurium is associated with less histamine release than atracurium. A dose of 0.15 mg/kg provides excellent intubation conditions after 120 s in infants anesthetized with nitrous oxide-thiopental-fentanyl anesthesia [119]. In the same study, the onset time was more rapid and the recovery time greater in younger patients.

Nitrous Oxide

In children, odorless N_2O speeds induction of anesthesia with sevoflurane, without substantive respiratory or hemodynamic adverse effects [122]. However, nitrous oxide may not be ideal for anesthesia in the neonate for the several reasons. First, many surgeries in neonates are emergencies that involve bowel obstruction or a risk of bowel distention, hence N_2O is often relatively contraindicated. Second, loss of the neonatal airway during induction of anesthesia with N_2O speeds the rate of desaturation as the ratio of oxygen consumption to pulmonary oxygen reserve would be very large. Third, N_2O has been shown to stimulate opioid and adrenergic centers that activate descending inhibitory neurons (DINS) in adults. These DINS transmit from supraspinal centers in the brain to the posterior horn of the spinal cord. When activated, DINS provide potent antinociception. In the neonate, DINS are poorly developed and immature [123], thus limiting the analgesic effects of N_2O [124]. Fourth, N_2O potentiates the neurotoxicity of other anesthetic agents on the developing brain in neonatal animals [125], although there is no evidence that N_2O is neurotoxic in humans. Fifth, when administered concomitantly with propofol or sevoflurane, N_2O decreases the regional oxygen extraction fraction and creates a possible imbalance in the cerebral metabolic rate [126].

In conclusion, the combination of propofol, opiates, or muscle relaxants to an inhalational induction provides better conditions for tracheal intubation and permits the use of smaller concentrations of sevoflurane, although the optimal doses of these compounds have not yet been determined in neonates.

Tracheal Intubation: Oral or Nasal Route?

The decision to intubate the trachea in the neonate orally or nasally is often an institutional or clinician's preference, based on local practice and experience.

Oral tracheal intubation is quicker [127] and easier to perform than nasal intubation, thereby reducing the period

of apnea and the time interval during which the airway is unprotected. A Cochrane review of nasal versus oral tracheal intubation in neonates in the neonatal intensive care unit yielded only two studies, precluding any definitive recommendations [128]. Nonetheless, the hemodynamic responses were similar when hypnosis and analgesia were provided, failed intubation occurred more frequently after nasal compared with oral intubations, and atelectasis occurred more frequently after nasal intubations [130].

Mobility of orotracheal tubes during head movement may be greater than that of nasotracheal tubes, although Cochrane review of two trials reported that the incidence of complications, including accidental extubation, was similar with nasal and oral intubations [130]. Published studies in neonates and preterm infants (560–2000 g) with orotracheal tubes demonstrated that 55° flexion of the neck yielded less movement of the tip of the tube than 55° extension of the neck (3.1 versus 7.4 mm) [119–131]. In 15 neonates and infants, aged 14 days to 15 months, extension of the neck displaced the tip of the orotracheal tube 6.5 mm in the cephalad direction, almost twice the 3.5 mm displacement of the nasotracheal tube [132]. Thus, movement of the tip of the tube in the trachea is greater with orotracheal intubation. Given the short length of the trachea in neonates (4–4.5 cm), extension of the neck in a neonate with an orotracheal tube could lead to an unexpected extubation.

In conclusion, the use of oro- and nasotracheal tubes in neonates appears to have advantages and disadvantages. Nasotracheal intubation tends to be more difficult and takes more time, thereby increasing the risk of desaturation, although it is more secure, and the trachea is less likely to be extubated than orotracheal intubation. In contrast, orotracheal intubation is easier, faster, but may facilitate more accidental extubations. Carefully taped tracheal tubes minimize excessive tube displacement, although nasotracheal tubes are associated with less displacement. The final decision to employ oral or nasotracheal intubation depends on the clinician's experience, the size of the infant, the context of surgery, and the postoperative destination of the infant.

Rapid Sequence Induction for General Anesthesia

RSI is indicated for every child who has a full stomach to minimize the risk of regurgitation of gastric contents and possibly pulmonary aspiration. To minimize these risks, induction of anesthesia may be delayed in the case of nonurgent procedures, although in cases that are more urgent, the anesthetic should proceed with an RSI.

Current fasting rules were developed based on the best estimate times for gastric emptying. Clear fluids may be ingested up to 2 h before anesthesia/surgery in neonates [133–136]. Breast milk may be up to 4 h before anesthesia, and artificial milk (e.g., cow's milk) up to 6 h before anesthesia [135–137]. A recent consensus statement on clear fluid fasting for elective pediatric general anesthesia (not including neonates) reduced the fasting interval after clears from 2 to 1 h before surgery, although this has been challenged [138–140]. If it is necessary to start surgery before the stomach is predicted to be empty, an RSI should be performed. The only metric that may yield insight into the time interval for gastric emptying after an injury or trauma in a child is the time interval between last food ingested and the trauma or insult [141]. These data have little impact on the clinical scenarios that present in neonatal surgery.

Some conditions associated with functional or mechanical ileus in the neonatal period require an RSI, independent of the fasting interval. These include disorders of the digestive tract: atresia, obstruction, volvulus or perforation, necrotizing enterocolitis, omphalocele, gastroschisis, and congenital diaphragmatic hernia. In the first month of life, infants with gastroesophageal reflux, untreated or persistent, may also be candidates for RSI. Pyloric stenosis, which usually occurs at the end of the first month of postnatal life, is certainly a condition with "full stomach." It would be extraordinary that a neonate with a full stomach does not present with intravenous access already established. Nonetheless, inhalational inductions have been performed in some centers for infants with full stomachs without substantial consequences! [142]

Preoxygenation

Preoxygenation is an essential component of an RSI. The aim of preoxygenation is to maximize oxygen reserves to preclude significant desaturation during the apneic period when anesthesia is induced, and the trachea is intubated. The frequency of desaturation during uncomplicated tracheal intubation in neonates is 42% and increases to 75% in difficult intubations [143]. This subject has been poorly investigated in neonates. Nonetheless, some pediatric studies have included infants less than 1 year of age and it is their data that we can extrapolate to predict the effects preoxygenation on desaturation during intubation in neonates.

The younger the age of the infant, the more rapidly they desaturate occurs once the facemask has been removed. In healthy infants whose lungs were ventilated manually, the saturation decreased from 100 to 95% in approximately 90 s after the onset of apnea and then from 95 to 90% in <10 s [144, 145]. In infants, 15 months of age, the time to desaturation to <95% after 2 min of preoxygenation was 110 s. Desaturation to <90% occurred as briefly as 8 s later [146]. An end-tidal oxygen fraction of 0.9 should be used as the target end-point for preoxygenation in infants 0–6 months of age to ensure denitrogenation 36 ± 11.4 s or ~60 s to become fully preoxygenated [147]. Despite preoxygenation with a tightly applied facemask, we should anticipate desatura-

tion to occur after a short interval of apnea if a supplemental source of oxygen is not provided.(see below)

Gastric Emptying

Passing an oro- or nasogastric tube before an RSI is neither required nor is it effective in completely emptying the stomach. However, a gastric tube may be useful in the presence of preoperative ileus or intestinal obstruction. Since neonates are exclusively fed liquids, a gastric tube may significantly reduce the volume of the gastric fluid contents, although pulmonary aspiration may still occur.

If a gastric tube is in place, it is not necessary to remove it before induction [148]. Its presence does not reduce the effectiveness of cricoid pressure [149]. The anesthesiologist may, however, prefer to remove the gastric tube to ensure clear visualization of the larynx.

Cricoid Pressure

Cricoid pressure has been an integral component of RSI in all patients at risk for pulmonary aspiration who require general anesthesia although its role and efficacy have been challenged lately, particularly in children [150]. However, cricoid pressure has caused several clinical problems when excessive pressure was applied and incorrect location and inappropriate timing [151, 152]. Cricoid pressure must be applied precisely if it is to be effective and atraumatic. However, several studies have demonstrated that cricoid pressure is not applied directly to the cricoid ring, is applied with inadequate force to occlude the esophagus, and that the esophagus and vertebral bodies are not flat and perfectly aligned [153–156]. Although the recommended force to occlude the lumen of the esophagus in adults is 30–44 N [157], bronchoscopic examination of the cricoid ring in neonates demonstrated that a force as little as 5 N force can reduce the lumen of the cricoid ring by 50% [158].

Even if cricoid pressure were correctly applied and completely occluded the lumen of the esophagus, there is no evidence that RSI prevents gastric fluid aspiration [159, 160]. In one study of 63,180 pediatric general anesthetics, the authors reported 24 instances of aspiration despite the application of cricoid pressure during induction of anesthesia [161]. Most recognize that cricoid pressure also impairs the view of the glottis during laryngoscopy [149, 160, 162, 163]. This is of particular relevance in neonates and infants in whom the adult hand that applies the pressure can limit the extent of the mouth opening, rendering laryngoscopy and intubation difficult. In addition, a relatively small force applied to the neck might cause subglottic obstruction with difficulty passing the tracheal tube [158]. If tracheal intubation is impeded for any of the above reasons, cricoid pressure must be released immediately to facilitate a rapid tracheal intubation, which remains the top priority for an RSI. On balance, clinicians continue to implement all aspects of a modified RSI in neonates at risk for pulmonary aspiration, although cricoid pressure is now infrequently applied [150, 164].

Mask Ventilation

Although mask ventilation with oxygen is not usually recommended during an RSI in order to avoid gastric insufflation and regurgitation, it must be performed if severe hemoglobin desaturation occurs before the trachea is intubated. Neonates should never be allowed to become hypoxic out of concern that mask ventilation might theoretically inflate the stomach and trigger regurgitation and pulmonary aspiration. The frequency of pulmonary aspiration during and after an RSI in infants and children is exceedingly rare, whereas the incidence of hypoxemia and their harmful sequelae are much more frequent. Without adequate preoxygenation, severe desaturation can occur in the healthy neonate within 10 s of apnea. This is often too brief an interval to complete induction of anesthesia, neuromuscular blockade, and tracheal intubation. Hence, many advocate ventilating the lungs manually after induction of anesthesia during RSI in neonates, limiting the peak airway pressures to <10 cmH_2O to avoid desaturation without inflating the stomach [165–168].

High-flow nasal oxygen therapy, which extends the safe apnea time of adults undergoing upper airway surgery and during tracheal intubation, is currently being studied in neonates and infants. This technique, which might be very relevant in neonate to decrease incidence of hypoxemia during tracheal intubation, is currently under investigation [169]. Blended oxygen/air flow rates of 70–80 L/min have been used in adults, which, when scaled down for size in neonates, correspond to 9 L/min flow. These flows not only extended the duration of apnea without desaturation in adults, but also attenuated or prevented the increase in carbon dioxide during the apnea period. With the ability to maintain saturation as well as ventilation, the technique was termed THRIVE or transnasal humidified rapid insufflation ventilatory exchange. However, when applied to young children, THRIVE has only maintained their oxygen saturations, it did not clear carbon dioxide from the lungs. The ongoing SHINE trial should shed further evidence on the utility of this technique in neonates when the results are published [169].

Anesthetic Agents for RSI

The RSI classically associates adequate preoxygenation and the administration of a hypnotic and a neuromuscular-blocking agent in predetermined doses in rapid sequence intravenously. The objective is to minimize the interval between the loss of upper airway protective reflexes and tracheal intubation, when the risk of pulmonary aspiration is greatest.

Intravenous hypnotics such as *thiopental* (3–5 mg/kg) (where available) or *propofol* (2–3 mg/kg) can be used for an

RSI, although the induction dose of propofol in neonates has not been determined. The ED_{50} for thiopental in neonates (to tolerate a facemask for 30 s) is 3.4 ± 0.2 mg/kg [170].

In neonates, *thiopental* allows a quick and smooth induction of anesthesia and preserves hemodynamic stability [171] In the first postnatal month, the dose requirement for thiopental is 45% less than in older infants 1–6 months of age, probably attributable to the reduced protein binding, more permeable blood-brain barrier, and increased brain sensitivity to thiopental [170]. However, the elimination half-life of thiopental in neonates exceeds 14 h, 2.5-fold greater than midazolam [172]. Hence, continuous infusions of *thiopental* are eschewed. When administered with succinylcholine, *thiopental* increases the success rate and shortens the time interval to tracheal intubation [173]. *Propofol* has a similar onset time to that of thiopental, but a much briefer duration of action, which is an advantage in RSI. *Propofol* is also more effective than *thiopental* in limiting the hypertensive response to laryngoscopy in children 1–6 months and to reduce the delay before extubation although comparable data in neonates has not been forthcoming [174]. *Propofol* confers two additional advantages over *thiopental*: it attenuates airway reactivity and decreases the muscular tension of the jaw muscles. When associated with succinylcholine in healthy children 0–3 months undergoing pyloromyotomy, propofol caused only a moderate decease in blood pressure [175]. Propofol may exaggerate right-to-left shunting in the immediate neonatal period (via a patent foramen ovale, ductus arteriosus), because it reduces systemic vascular resistance more than pulmonary resistance [176]. When used in preterm neonates (30 weeks gestational age, <8 h postnatal age) in a dose of 1 mg/kg IV bolus, propofol decreased the mean arterial blood pressure by 33%, from 38 (29–42) mmHg to 24 (22–40) mmHg [177]. This decrease in systemic blood pressure is similar to that associated with one MAC inhalational anesthetics in neonates [178, 179]. Administration of 10–20 mL/kg boluses of balanced salt solution before administration of propofol (and inhalational anesthetics) may attenuate these hemodynamic effects. In neonates and infants, propofol allows fast intubation and reduces anesthesia induction time compared with sevoflurane [180]. Pain during IV injection of propofol into a small vein, for example, in the hand, is common in neonates, leading to a brisk withdrawal of the extremity. This may lead to accidental disconnection or loss of the line, at a critical stage of induction. Several strategies have been shown to be effective to attenuate the pain during injection including administration of nitrous oxide by mask and a mini-Bier block with lidocaine [181–183]. In the absence of effective preventative treatment, the anesthesiologist should secure the limb gently while propofol is injected and until the neonate is deeply anesthetized.

For RSI, *ketamine* has not been embraced for induction, because it may increase systemic blood pressure and cerebral blood flow in premature infants. However, in the case of neonates who are full-term and hemodynamically unstable, IV ketamine is a suitable choice.

Succinylcholine (2 mg/kg) is the muscle relaxant of choice for RSI because of its rapid onset and brief duration of action [184]. The younger the child, the briefer the duration of the paralysis after succinylcholine [185]. All muscle relaxants, especially succinylcholine [173, 186], greatly improve the conditions for tracheal intubation [78]. However, life-threatening side effects have caused many to fear the use of succinylcholine in young children [77]. Bradycardia may occur after a single dose of IV succinylcholine in infants, but is obviated by pretreatment with 0.02 mg/kg IV atropine. More ominously, acute hyperkalemia and rhabdomyolysis may occur after succinylcholine when it is administered to a neonate with an undiagnosed myopathy, such as Werdnig–Hoffman disease or muscular dystrophy. Although these diseases are rare, if electrocardiographic evidence of hyperkalemia occurs after succinylcholine, IV calcium chloride (10 mg/kg), not dantrolene, should be administered intravenously. Malignant hyperthermia (MH) is an exceedingly uncommon disease in neonates and does not present at induction of anesthesia with ventricular arrhythmias, although succinylcholine should be avoided where a family history of MH is catalogued.

Rocuronium has emerged as the intermediate muscle relaxant of choice in infants and children when succinylcholine is contraindicated or eschewed. Although doses as large as 0.9 mg/kg IV provide excellent conditions for tracheal intubation in less than 1 min, the age of the children in that study exceeded 1 year [187]. In contrast to succinylcholine, the duration of action of rocuronium increases with greater doses and younger age patients. The optimal dose of rocuronium for RSI in neonates has not been determined. Published studies indicate fairly rapid onset times with 0.45 and 0.6 mg/kg IV rocuronium, although these doses were studied in the presence of inhalational anesthetics [116]. The downside to using large doses of rocuronium in neonates is the prolonged time to recover: 62 and 95 min, respectively [77, 116]. If the surgery is expected to be brief, as in a pyloric stenosis, then the use of large doses of rocuronium will markedly delay emergence and extubation. The prolonged duration of action of rocuronium must be considered when choosing both the neuromuscular-blocking agent and its dose, although the availability of sugammadex to rapidly antagonize the action of high-dose rocuronium has made this issue moot (see below).

With the increasing use of propofol in neonates and during RSI, anticholinergics may continue to play a substantive role. Propofol enhances parasympathetic activity, which

can explain the bradycardia often observed after induction of anesthesia. Since cardiac output depends to a large extent on heart rate in neonates, bradycardia will compromise the cardiac output and decrease tissue oxygenation. Atropine in a dose of 20 mcg/kg IV may be used to maintain a rapid heart rate, without a minimum dose [188]. In addition, neonates are prone to developing hypoxemia during prolonged apneas such as during RSI,; hence, a modified RSI is preferrable [167, 168]. For both of these reasons, intravenous atropine is an appropriate adjunct and should be integrated in the modified RSI in neonates.

Maintenance of Anesthesia

Hypnosis

Short-acting inhalational anesthetics are appropriate hypnotics for maintenance of anesthesia in neonates (See Chap. 3). Sevoflurane offers several advantages over intravenous anesthetics in that it is suited for an inhalational induction, is minimally metabolized, has rapid pharmacokinetics, and is safe in infants with cardiorespiratory disease. Sevoflurane does potentiate neuromuscular-blocking drugs (NMBDs) [113], which means that smaller doses of NMBDs may be required to achieve comparable twitch depression. Desflurane is unsuited for inhalational induction, because it is irritating to the supraglottic and glottic structures as well as causes bronchoconstriction [189] although it has more favorable pharmacokinetics primarily on the basis of its minimal solubility in blood and tissues. This latter characteristic leads to a more rapid return to spontaneous respiration and recovery compared with the older, more soluble anesthetics. Desflurane is also metabolized 10-fold less than sevoflurane in vivo, resulting in virtually no end-organ toxicity. However, carbon monoxide may be liberated into the breathing circuit if desflurane (and isoflurane) is incubated with desiccated CO_2 absorbent [190, 191]. The minimum fresh gas flow should be used with all inhalational anesthetics to limit their impact on the environment.

Many have questioned the need for inhalational anesthetics for neonatal surgery given the primary goal is to deliver stress-free analgesia. Under these conditions, there is no need to introduce an inhalational anesthetic for maintenance as its impact is more than likely to lead to hypotension and/or bradycardia. Moreover, neonates do not have cortical recall, so ensuring amnesia is not a primary objective of anesthesia. In neonates, many have experienced difficulty maintaining circulatory homeostasis when an opioid and inhalational anesthetic are combined, whereas an opioid-based anesthetic confers a stress-free anesthetic and adequate postoperative analgesia in the NICU or PACU.

Maintenance of anesthesia via the intravenous route in neonates has been fraught with pitfalls for several reasons [192]. First, the IV lines are particularly fragile in neonates and, as such, introduce the risk of technical problems. Subcutaneous infiltration or accidental disconnects may occur most dangerously during maintenance of anesthesia and under the drapes. This is particularly problematic with IVs sited in the antecubital fossa, which preferably should be switched to hand or foot IVs to preclude undetected intramuscular or subcutaneous infiltration. Moreover, once the drapes cover the neonate, and surgery begins, the IV site is often concealed from the anesthesiologist's sight and control. Most infusion pumps will alarm to an occluded line although drip IV sets will continue to infuse interstitial fluid. All lines should have luer lock connections to ensure continuity of flow and protection from external pressure. There are no simple monitoring devices that can alert the anesthesiologist to a disconnected intravenous catheter. As a result, the patient might awaken, move, or display pain-related hemodynamic disturbances while presumed to be anesthetized if a disconnect occurred during surgery and under the drapes.

Second, the effect-site concentration of propofol during anesthesia cannot be measured, unlike the breath-by-breath data provided by the gas analyzer for inhalational anesthetics. The pharmacokinetic profile of propofol in the first weeks of life has received little attention, but recent evidence indicates that marked interindividual variability (due to age) and a marked reduction in clearance in part attributable to immature activity of phase 1 and II enzymes may hold the keys to predictable infusions [193–195]. An important covariate in determining the dose of propofol is the postmenstrual and postnatal ages. Specifically, the clearance appears to be diminished with decreasing postmenstrual and postnatal ages (> or <10 days). Surprisingly, the induction dose of propofol in neonates has not been reported, although modeling suggests that reduced induction doses (1.5–2 mg/kg) may portend anesthetic concentrations when followed by infusion rates that are less than those recommended in older children [196, 197].

Third, isolate case reports of profound hypotension and near-cardiac arrest has been reported with induction doses of propofol or postoperatively after a single bolus of propofol, anesthesia [176, 198]. The pathogenesis of these isolated reports of near-cardiac arrest remains unclear, although exacerbation of a right-to-left shunting through a patent foramen ovale or ductus arteriosus after the propofol bolus was not ruled out. Hypotension has also complicated a dose-finding study for propofol for tracheal intubation in the neonate [176]. Given this history and that most neonates are relatively dehydrated in the NICU, it may be prudent to pretreat neonates with 10 mL/kg IV balanced salt solution before administering an IV bolus of propofol. Another relative propofol overdose in neonates occurred after the induction dose was followed by an infusion [199]. This may be attributed to a failure to appreciate the profoundly reduced

clearance of propofol, possibly as little as 10% of the adult clearance in some subgroups of neonates [197]. To date, propofol infusion syndrome reported has been reported in only a single neonate, and that occurred in the original description of the syndrome in 1992 [200, 201]. This may be the result of the proscription of propofol infusions in infants based on the early reports of the syndrome. A systematic review of propofol use in neonates and infants cautioned practitioners to monitor for apneas as the most common sequela in this age group [201]. In the absence of a reliable device to monitor the depth of anesthesia, neonates may be under- or overdosed with propofol, which cannot be extracted from the bloodstream once administered unlike inhalational anesthetics. Given this experience, neonates who present for general anesthesia should receive a fluid bolus before induction of anesthesia. IV atropine and epinephrine should be immediately available for resuscitation as needed.

Analgesia

Forty years ago, neonates underwent surgery with little to no analgesia. In the 1980s, several investigators defined the capability of the human neonate to perceive pain and demonstrated the importance of preventing pain (see Chap. 15). Indeed, further research uncovered that the neonate is actually more sensitive to painful stimuli than older subjects [202, 203]. First, several seminal studies documented the short-term consequences of pain (and the stress response) in the neonate in terms of changes in hemodynamics, metabolism, agitation, and recovery [204, 205]. Second, subsequent studies determined that painful experiences such as neonatal circumcision caused long-term behavioral changes [206]. Some of these early painful experiences resulted in persistent alterations in pain sensitivity [207, 208].

How could a child or adult "remember" a painful neonatal experience? Pain sensitivity and behavioral changes depend on "implicit memory." Pain-induced *neurotoxicity* and *neuroplasticity* can account for some of the symptoms. Unrelieved neonatal pain causes apoptosis in cortical and subcortical areas, associated with abnormal neurocognitive development in rats [209]. Interestingly, the development of memory was also impaired in this model. Changes caused by early painful experiences can also be observed in the peripheral nervous system: neonatal skin wounds caused a prolonged increase in the innervation of the wound site in rats [208]. In a study using functional MRI, pain-specific cortical and subcortical hyperactivation was demonstrated in children 11–16 years of age, who were born preterm, and who had undergone painful procedures as neonates [210]. Finally, a painful stimulus may activate the amygdala even during general anesthesia, thereby increasing the probability of recall, even if subconscious.

Once the negative consequences of untreated pain were strongly established, clinicians increased their use of perioperative analgesics in neonates. In the past two or more decades, the attitudes of anesthesiologists and other physicians have changed radically shifting from "no analgesia" to "as much analgesia as possible" for neonates. The dose of analgesics administered is limited only by eliminating pain and/or the presence of side effects, most notably respiratory depression.

In terms of the pharmacokinetic profiles of opioids in neonates, large interindividual variability precludes a relationship between the opioid concentrations and the effect site. Compared with adults, protein binding of opioids is diminished, free fractions are increased, the blood-brain barrier is more permeable, distribution volumes are increased, clearances are decreased, and elimination half-lives are greater in neonates than in older children [211]. Protein binding and hepatic metabolism undergo dramatic changes and maturation throughout the neonatal and infant periods. Alpha-1-acid glycoprotein (AAG) is the main binding protein for fentanyl, sufentanil, and alfentanil [212]. Neonates and young infants have reduced concentrations of AAG, which explains, in part, the greater free fraction and larger volumes of distribution of these opioids [213].

At birth, most metabolic pathways are immature, especially those involving hepatic enzymes [214]. The CYP450 3A4, which is a major hepatic enzyme of the metabolism of fentanyl and sufentanil, is nonfunctional at birth (replacing the fetal CYP3A7 isozyme) [215], but matures rapidly during the first weeks of life [214, 216]. Moreover, many of the P450 cytochromes are subject to genetic polymorphisms that can modulate their activity [217]. The maturation processes, combined with the genetic variability, result in important interindividual differences in the responses to opioid during the neonatal period.

In neonates, *fentanyl* and *sufentanil* are the most frequently used opioids during general anesthesia. Both opioids provide relative hemodynamic stability [218]. When used in a single-dose before tracheal intubation, both IV fentanyl (1–5 μg/kg) and sufentanil (0.2–0.3 μg/kg) have a rapid onset of action and a short duration of action. In contrast, the pharmacokinetics of sufentanil makes it a more appropriate opioid for maintenance of anesthesia: if used in repeated injections or by continuous infusion, fentanyl may accumulate in peripheral tissues (fat, muscle) as its context-sensitive half-life increases as the duration of the administration increases [219]. To offset accumulation, the drug dose should be tapered over time. Accumulation of the fentanyl is even more pronounced in neonates because of the immaturity of metabolic pathways.

Alfentanil's rapid onset and short duration of action are of interest when it is used as a single dose for brief surgical procedures. In the neonate, pyloric stenosis is a good indication for this opioid. Theoretically, alfentanil can be delivered as a continuous infusion, but its short duration of action is no lon-

ger an advantage over fentanyl or sufentanil. Like fentanyl, alfentanil accumulates in a large peripheral compartment, with an increasing context-sensitive half-life as the infusion continues [219].

Also, it is metabolized by the same cytochromes as fentanyl and sufentanil and, thus, is susceptible to the same interindividual variability through genetic and developmental variability.

Remifentanil is an ultrashort-acting opioid that is rapidly metabolized by tissues esterases (that are mature at birth) to inactive metabolites. Remifentanil achieves its maximum end-organ effect rapidly after the infusion begins. Not surprisingly, these characteristics lead to a context-sensitive half-life that is constant, independent of its duration of infusion, even in neonates and infants [220]. However, evidence suggests that the rate of recovery after remifentanil in neonates less than 1 week of age may be slower than in infants 1 week to 3 months of age [221]. Pharmacodynamically, remifentanil may induce bradycardia, an effect classically attributed to the parasympathomimetic properties of remifentanil, a direct negative chronotropic effect [222]. The decrease in heart rate attributable to remifentanil after 5 μg/kg was infused over 1 min, peaks at 3 and 5 min after the infusion, but was less impressive in infants ≤2 months than in older children, although only 8 infants ≤2 months were included [223].

In terms of using remifentanil during maintenance of anesthesia, several issues persist. Pharmacokinetic models integrated in electronic devices for neonates have not been developed. Furthermore, chest wall rigidity and postoperative hyperalgesia remain concerns after IV boluses of the opioid.

In conclusion, the choice of the optimal analgesic for general anesthesia in the neonate depends on the type and duration of surgical procedure as well as the postoperative pain that is anticipated and whether airway management is expected, that is, rapid extubation or continued ventilation.

Although the neurotoxicity of NMDA antagonists and $GABA_A$ agonists in animal models are a cause for concern, until further data are available in humans (see Chap. 18), we do not recommend a change in practice. We strongly recommend the use of potent opioids such as fentanyl or sufentanil, although the use of remifentanil is increasing. Growing interest about the properties of remifentanil and abundance of clinical trials in neonates might soon allow its safe use in this age group. Until reliable and valid pain/analgesia monitors are developed, it remains difficult to distinguish between "not enough" and "too much" analgesia.

Muscle Relaxants

In the past, when pain and recall were neglected concepts in the neonate, the use of muscle relaxants was commonplace. But muscle relaxants fell into disfavor in the NICU when it became apparent that paralyzing infants resulted in contractures that were difficult to reverse. Furthermore, the introduction of newer and safer opioids and hypnotics for sedation replaced the need for paralysis to facilitate ventilation [224–226]. In some instances, anesthesiologists' fears of residual neuromuscular block and/or incomplete antagonism with anticholinesterases led many to restrict the use of NMBDs for tracheal intubation. However, nondepolarizing NMBDs may also improve surgical conditions during surgery, although the indications are quite few. If NMBDs are required during critical periods of surgery, bolus doses are preferred over infusions. If NMBDs are administered, neuromuscular monitoring should be used. Alternately, bolus doses of propofol have proven to be very effective to "relax" the abdomen when it appears to be tight, or the bowels will not return easily to the abdomen as the surgery concludes. Although untested, this approach to relax the abdomen with propofol is exceedingly effective, does not delay emergence, and is ubiquitously used. If NMBDs are used, it is imperative to appreciate that the doses are smaller and even these smaller doses may confer exaggerated effects with a less predictable duration of action.

The release of sugammadex has changed anesthesiologists' reticence toward using rocuronium and vecuronium in neonates [112]. Sugammadex irreversibly binds both NMBDs and excretes them via the kidneys. Current evidence in neonates and infants indicates that sugammadex is well tolerated in neonates using similar dosing as in adults [107]. Sugammadex has not been associated with any side effects except for hypersensitivity, which has not been reported in neonates up to now.

Conclusion

There are many controversies in neonatal anesthesia, and in this chapter, we sought to explore several of these. In doing so, we have outlined both the advantages and disadvantages of each approach, what is known and unknown about the evidence, and where future studies are most needed.

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Airway Management

5

Annery G. Garcia-Marcinkiewicz, Paul A. Stricker, and John E. Fiadjoe

Expertise in neonatal airway management requires an understanding of early human anatomical development as well as a set of clinical skills to provide safe mask ventilation and tracheal intubation in this extremely small-sized population. Since neonatal airway experiences are not a daily occurrence in most anesthesiology training programs, this skill set is acquired only after repeated patient encounters over a span of many years or decades. In this chapter, we review the foundations upon which management of the neonatal airway is based. The chapter is divided into three sections: (1) anatomy and physiology of the neonatal upper airway, (2) techniques for standard neonatal airway management, and (3) techniques for managing the anatomically abnormal neonatal airway.

Upper Airway

Anatomy

The unique anatomical features of the upper airway in the neonate define the special considerations required to maintain a patent airway. The occipital portion of the neonatal skull is relatively larger than that of older infants and children (neurocranium-to-face size ratio is 8:1 in neonates, 6:1 in 2-year-olds, and 4:1 in 5-year-olds [1, 2]). This anatomical feature results in a natural state of cervical flexion that facilitates direct laryngoscopy in the supine child [3] but may predispose to upper airway obstruction during spontaneous and mask ventilation [4]. Many neonatal and pediatric textbooks have emphasized the existence of obligate nasal breathing in neonates, as a means to facilitate and coordinate the suck-swallow-breathing mechanism. Although neonates born with congenital choanal atresia occasionally develop life-threatening upper airway obstruction [5], healthy neonates readily convert to mouth breathing [6].

A notable anatomical feature of the neonatal airway is the relatively cephalad position of the larynx (i.e., with the uvula in close proximity with the epiglottis) that facilitates the swallowing-breathing mechanism. As the infant grows, the position of the larynx moves caudally from the C2–C3 level in the infant to the C4–C5 level by 3 years of age. This increases the distance between the larynx and the mouth [7]. The location of the tip of the epiglottis also changes from the C2 level to the C3 level [8]. This more cephalad position of the larynx in the neonate dictates that an optimal direct view of the glottic aperture will be obtained with a straight rather than curved laryngoscope blade [9].

The high compliance of the neonatal chest wall (due to incomplete ossification of the ribs and weak intercostal muscles) limits the passive outward recoil that contributes to maintaining the functional residual capacity (FRC) in older children. Thus, neonates can only preserve their FRC volume by using their laryngeal adductor muscles as expiratory "valves" to restrict exhalation and maintain positive end-expiratory pressure, a process referred to as "laryngeal braking" [10–12].

Reflexes

Upper airway reflexes protect against the inhalation of foreign substances into the lower respiratory tract. Although these neonatal reflexes have been studied in both the awake and sedated states, much less is known about their state at deeper levels of anesthetic-induced unconsciousness.

In children beyond early infancy, mechanisms that protect against the ingestion of foreign materials into the lower respiratory tract include swallowing and coughing [13]. Neonates

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and young infants, however, primarily gain this protection by central apnea (with bradycardia), upper airway obstruction [14], laryngospasm, and arousal [15]. Laryngeal chemoreflexes mature rapidly during early development [16]. These adaptive responses are more prominent the more premature the neonate [14, 17–22] and may play a role in the etiology of sudden infant death syndrome (SIDS) [23]. The apneic reflex (with bradycardia) may be prolonged in the presence of sedative or anesthetic agents [24–26], hypoxemia [27, 28], anemia [29], and RSV infection [30, 31]

Airway Management

Airway management in neonates presents challenges that are unique to this age group. Neonates usually require emergency procedures; thus, the issues that pertain to the urgent nature of the intervention add to the difficulties and risks. In this section, we address the special considerations when managing the neonatal airway during the perioperative period.

Anesthesia

Preanesthetic Assessment

Assessment of the neonate in the preanesthetic period includes a thorough review of the previous encounters in managing the airway. If tracheal intubation has been performed previously, the involved providers should be queried and the medical records reviewed to clarify how the airway was managed and the difficulties encountered. For all neonates, the underlying diagnoses and conditions should be reviewed with specific attention to the upper and lower airways, since the management may have to be tailored accordingly. Some conditions that lack direct airway involvement may have implications for airway management. For example, the neonate with a giant omphalocele may rapidly desaturate during induction of anesthesia due to pulmonary hypoplasia and a reduced FRC. Similarly, neonates with congenital diaphragmatic hernia require special attention to limit the peak inspiratory pressures during induction of anesthesia to prevent intestinal insufflation during mask ventilation and/or a pneumothorax after tracheal intubation.

Physical examination of the airway should focus on the presence of anatomical abnormalities that may hinder facemask ventilation or laryngoscopy. Physical findings such as micrognathia should alert the anesthesiologist to prepare appropriate instruments to secure a difficult airway. Diagnosing micrognathia in neonates may be tricky; careful examination of the facial profile with the neonate in the neutral position may reveal a mandible that is recessed with respect to the maxilla.

Preoperative Preparation

All equipment that may be required to manage the airway should be prepared before the neonate arrives in the operating room or before anesthesia is induced for procedures in the neonatal intensive care unit. Induction agents and emergency medications (as appropriate) should be prepared in unit doses to reduce drug errors should an urgent intraoperative situation ensue. The laryngoscope should be checked together with backup equipment before induction of anesthesia. A tracheal tube (TT) of suitable size, as well as ones that are one-half size smaller and one half size larger, should be available. Appropriately sized oral airways for managing upper airway obstruction should be obtained. Because of its important role as a ventilation rescue device, a laryngeal mask should also be immediately available. If difficulty with facemask ventilation or tracheal intubation is anticipated, additional equipment and personnel should be available as detailed later.

Airway Management and Equipment

Face Mask Ventilation

The neonate should be positioned supine to facilitate mask ventilation and direct laryngoscopy. The head should not be raised off the bed, but may be supported by a circumferential head ring [3]. The selected mask size and fit should be checked before induction of anesthesia. A properly sized mask covers the nose and mouth without overlying the eyes or extending beyond the chin. After loss of consciousness, upper airway obstruction is relieved primarily by a chin-lift maneuver, which is easily accomplished by applying the straightened middle (or long) finger of the left-hand across the bodies of the left and right sides of the mandible and extending the neck (Fig. 5.1). However, in anesthetized neonates, this maneuver closes the mouth, which may obstruct the upper airway, a problem often incompletely relieved by simply extending the neck. To complicate matters, digital pressure is often inadvertently applied to the submental triangle, which further obstructs the upper airway. An essential maneuver to establish a patent upper airway in neonates and young infants (in addition to what was mentioned above) is to sublux the temporomandibular joint, which is accomplished by placing the operator's fifth digit(s) in the retromandibular notch, at the apex of the ascending ramus of the

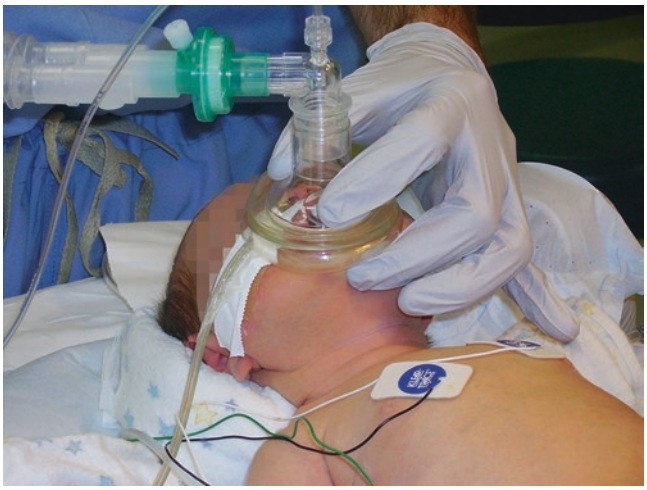

Fig. 5.1 When mask ventilating a small infant, the middle finger rests on the mandible to provide chin lift without compression of soft tissues in the submental triangle

mandible, immediately below the external auditory canal and behind the pinna. The condyle is lifted in an upward direction, toward the frontal hairline (i.e., a full "jaw thrust") [32]. This maneuver anteriorly translocates the jaw as well as rotates the temporomandibular joint in anesthetized neonates and infants, thereby opening the mouth and pulling the tongue off the posterior pharyngeal wall (Video 5.1). The facemask is then held on the face using the operator's thumbs. A far less effective "jaw-thrust maneuver" that is widely taught involves applying digital pressure to the angle of the mandible. In the latter maneuver, the mandible is translocated anteriorly, but the temporomandibular joint does not rotate and the tongue continues to lie against the hypopharyngeal wall. In contrast to Larson's retromandibular maneuver, this only partially relieves the airway obstruction. To maintain a patent airway while subluxing the temporomandibular joint, the long finger is placed at a crease at the base of the neck and swept upward to the mentum, creating "two chins". This holds the mandible subluxed and the airway patent while the fingers behind the pinna are removed. To confirm that subluxing the mandible opens up the laryngeal vestibule, Video 5.2 demonstrates movement of the supraglottic tissues when digital pressure is applied to the retromandibular notch of the ascending ramus of the mandible (Video 5.2).

When it is not possible to obtain a patent airway by repositioning and an effective jaw thrust, the next step is often to insert an oropharyngeal airway. However, if an oral airway is used, it is most important to select the correct size of the oral airway. An oral airway that is too large may push the epiglottis into the glottic opening, whereas an airway that is too small may push the tongue into the glottic opening. In the neonate with a difficult airway, the use of an oral airway may be even more precarious as it may worsen rather than improve the patency of the airway. Hence, it is crucial to understand how to optimize the upper airway by manipulating the temporomandibular joint rather than by only relying on oral airways.

In most neonates, effective facemask ventilation can be accomplished at peak inspiratory pressures of <15 cm H_2O and rates of 20–40 breaths per minute. Maintaining positive end-expiratory pressure during ventilation (5–10 cm H_2O) promotes alveolar patency and improves gas exchange. A rapid ventilation rate helps to maintain the FRC by limiting expiration. Occasionally, an alveolar recruitment maneuver is required (see below).

Laryngeal Mask Airways and Supraglottic Devices

Although tracheal intubation remains essential for safe intraoperative airway management during emergency surgery, some practitioners prefer a supraglottic airway device for elective surgery in neonates. However, initial studies and clinical experience with the Classic Laryngeal Mask Airways (LMAs) in neonates demonstrated a greater failure rate during insertion compared with larger size LMA s in older children [33]. This was attributed to an inappropriately designed cuff that failed to fit the different anatomy of the neonatal airway. Further clinical experience suggests that while placing an LMA is no more difficult in this age group than older children, these small LMAs may be dislodged more easily. Therefore, whenever an LMA is used, the capnogram must be observed continuously and the anesthesiologist prepared to intervene should the capnogram decay.

LMAs may offer advantages over tracheal intubation during resuscitation away from the operating room, because the LMA is simple to insert, requires technical skills that are easily acquired, and is associated with a high success rate, even in the hands of inexperienced operators [34]. Recent studies have demonstrated that the failure rate for tracheal intubation by resident pediatricians in the delivery room and NICU is substantial [35–38]. Evidence to date suggests that the LMA is effective in neonatal resuscitation in infants >34 weeks (>1500 g) and comparable to bag-mask ventilation [39, 40]. Also, the LMA was comparable with tracheal intubation, although the evidence was of low quality. There is a lack of evidence for the LMA infants <34 weeks gestational age. It remains to be established whether the LMA or other supraglottic airway should be used for primary airway management in neonatal resuscitation [41]. However, its use has been recommended as a secondary tool in near-term and term neonates who have failed resuscitation with bag-mask ventilation or tracheal intubation [42].

The ProSeal LMA is a reusable laryngeal mask airway with a wider laryngeal bowl and a channel for gastric drain tube insertion that runs lateral to the airway tube. The device is available in a size 1 and has been studied in neonates and infants weighing 2–5 kg [43, 44]. The initial results suggest that in addition to the 100% success rate inserting the ProSeal LMA [43, 44], the quality of the initial airway, the effectiveness of the seal, and the maximum tidal volume were significantly better than with the classic LMA [43, 44].

The LMA Supreme is a second-generation, single-use device [45]. It has an airway tube that is curved and is more rigid to facilitate insertion. The gastric channel runs central to the airway tube [45].

The Ambu Aura Gain is another second-generation LMA with a gastric drain channel and large cuff. When compared with the LMA Supreme, the Ambu AuraGain was found to have similar leak pressures in infants and children, with fewer airway maneuvers to maintain a patent airway [46].

Laryngeal tube suction II (LTS II; VBM Medizintechnik, Sulz, Germany) is another supraglottic airway device available in a size suitable for use in neonates. It is inserted blindly like the LMA. The LTS II has an esophageal and a pharyngeal cuff that are interconnected as well as a channel for placement of a gastric drain tube. Ventilation is delivered through multiple holes in the tube that are positioned between these two cuffs. While a case series describing the utility of this device in 10 neonates and infants has been published [47], larger prospective trials evaluating its safety or efficacy in neonates have not yet been conducted.

The LMA can be used as a valuable bridge to tracheal intubation in neonates with difficult airways. This will be reviewed in a later section of the chapter.

Laryngoscopy and Airway Instrumentation

Indications for tracheal intubation are traditionally determined by the surgical procedure, duration of the surgery, risk of aspiration of gastric contents, and pulmonary function. In anesthetized neonates, airway maintenance with a facemask is less desirable because of the high dead space-to-tidal volume ratio and concerns for the development of atelectasis. Tracheal intubation is indicated for all emergency surgery, open cavity procedures of the abdomen or chest, intracranial procedures, and in cases where control of arterial PCO_2 is required. It is also indicated when the anesthesiologist has limited access to the airway during surgeries such as those involving the head and neck and when positions other than supine are required. Tracheal intubation and mechanical ventilation are also useful in neonates to avoid atelectasis that could develop during prolonged anesthesia with spontaneous ventilation.

The "sniffing position" is classically described as the optimal head position to facilitate direct laryngoscopy and tracheal intubation in adults. In neonates, better alignment of pharyngeal structures is achieved with simple neck extension [48]. Because the occiput is relatively large in the neonate, their head is naturally in the "sniffing position" without active head flexion! If the large occiput of the neonate is placed on a pillow, the neck becomes flexed, which may contribute to airway obstruction. Although the use of a shoulder roll has been recommended when positioning the neonate before intubation, a recent randomized controlled trial confirmed that the glottic view in infants with a 2-inch shoulder roll was not improved compared with the view without a shoulder roll [49]. Positioning the neonate on a flat surface with a head ring that does not elevate the head is preferred.

Direct laryngoscopy is a widely used method for achieving tracheal intubation in neonates. Traditionally, the Miller blade was favored in this age group to facilitate the alignment of the oral and laryngeal axes [3]. This blade offers greater control and displacement of the base of the tongue, particularly for difficult intubation. The smaller size and reduced profile of the Miller blade (or the Wisconsin or Wis-Hipple size 0 blade) may also give the operator more room to pass the TT through the mouth and pharynx and into the trachea while maintaining the visual pathway. When laryngoscopy is performed with a straight blade, the blade is preferably introduced at the right side of the mouth, not in the midline, an approach known as the paraglossal approach, while pushing the tongue to the left [50, 51]. The blade follows the right alveolar groove until the tip reaches the epiglottis, at which point the epiglottis is lifted to expose the glottis. This approach yields a superior view of the glottis compared with that from a midline approach.

Until recently, there was no objective evidence to prove that the straight blade provides either an improved view or easier tracheal intubation when compared with the curved blade in neonates [52, 53]. Two recent randomized clinical trials in infants and children <2 years old reported that the Miller and Macintosh blades provide similar laryngoscopic views and intubation conditions [54, 55], although when the study was repeated in neonates, the glottic views with the Miller blade size 0 were superior to those with the Macintosh size 0 [56]. Traditionally, the Miller blade is advanced to lift the epiglottis to expose the larynx. Some,

however, use this blade in a manner analogous to the curved blade by advancing it into the vallecula to lift the tongue [54, 55]. In both neonates and older infants, lifting the tongue with the Miller blade provides similar views of the glottic opening [54, 56]. Care should be taken when placing the Miller blade in the vallecula as the tip of the blade, unlike the Macintosh blade, is not rounded [50, 57]. If the glottic exposure is suboptimal after advancing the laryngoscope and positioning it, the laryngoscopist can apply external, posterior pressure to bring the glottis into view. A few studies have described the clinical effectiveness of external laryngeal manipulation in facilitating tracheal intubation [58]. Adult studies have demonstrated that a small amount of external, posterior pressure with or without lateral displacement often significantly improves laryngeal exposure and facilitates intubation [59–61]. In neonates, laryngeal manipulation can be performed using the operator's fifth digit of the left hand (Fig. 5.2). Of note, a recent study in critically ill children found that external laryngeal manipulation during direct laryngoscopy was associated with a smaller initial tracheal intubation success [58].

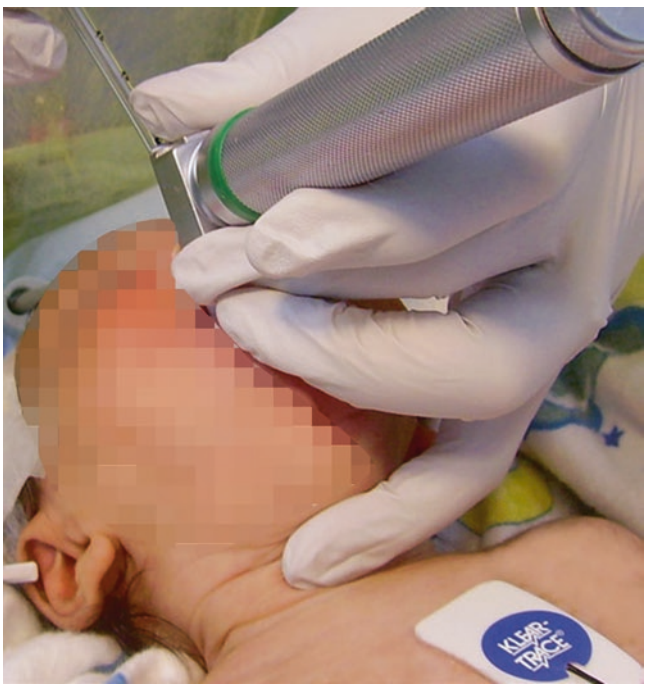

Fig. 5.2 Orotracheal intubation in the neonate is facilitated by using the fifth finger of the left hand, which provides posterior or lateral external displacement of the larynx

Orotracheal Intubation

In select circumstances and other than in the obstetric delivery room, tracheal intubation has been performed in unmedicated, awake neonates. Often this involved neonates who could not tolerate the cardiovascular depressant effects of anesthetic or sedative drugs or whose airways were compromised or potentially difficult to secure. This approach is now discouraged. Neonates, who perceive pain in response to a nociceptive maneuver, experience neural sensitization or hyperexcitability such that a subsequent laryngoscopy without sedative premedication or general anesthesia may result in untoward cardiovascular responses (and behavioral) effects and, thus, should be avoided whenever possible [62–64]. The administration of anesthetic, sedative, and neuromuscular-blocking drugs improves conditions for intubation, decreases the likelihood of trauma to the airway, and improves the first-pass success rate [65–68]. A consensus statement published by The International Evidence-Based Group for Neonatal Pain states "tracheal intubation without the use of analgesia or sedation should be performed only for urgent resuscitations in the delivery room or for life-threatening situations associated with the unavailability of intravenous access" [63]. In select circumstances such as difficult facemask ventilation, tracheal intubation may be performed after sedative premedication rather than general anesthesia. Various medication regimens have been evaluated for nonemergency tracheal intubation in neonates in the neonatal ICU [69–73]. However, most of these studies were quite limited, precluding the determination of an optimal regimen [74].

Nonetheless, tracheal intubation in an unsedated critically ill neonate may be a life-saving maneuver. Although it has been largely abandoned, if the need arises, it is important to know how to perform an "awake" intubation. This is not a technique that should be first attempted in a life-saving situation. When planning an awake intubation, the operator should ensure that the stomach is empty (e.g., suction is readily available), and atropine 0.02 mg/kg IV and oxygen have been administered. In advance of the intubation, a styleted TT of the appropriate size (in a hockey stick configuration), laryngoscope handle, and appropriate size blade, and suction should be prepared. Although it may seem intuitive that a styleted TT should facilitate tracheal intubation, a Cochrane review failed to prove that the success rate of tracheal intubation among pediatric trainees using styleted TTs exceeded that with nonstyleted TTs [75]. Evidence to support the benefit for stylets during tracheal intubation in

neonates remains lacking. An experienced assistant holds the infant's shoulders against the mattress while simultaneously fixing the head firmly in a central position. Alternately, the arms are hyperextended such that there are held against the side of the head to prevent the head and torso from wiggling and the shoulders from lifting off the table during laryngoscopy. Once laryngoscopy begins, tracheal intubation should be completed within 10–12 s. The laryngoscope blade should be inserted into the mouth at the right commissure aiming the tip of the blade toward the midline in one fluid motion. The laryngoscope should be held in one hand and the TT in the other. As soon as the neonate gags as the blade is inserted, the epiglottis should be lifted and the tube passed between the vocal cords. When carbon dioxide is detected, 2–3 mg/kg IV propofol or other anesthetics is administered to attenuate any cardiovascular responses to laryngoscopy. The TT should then be taped and secured at an appropriate depth. It is most important to instruct the assistant who is restraining the infant not to release the infant until notified to do so otherwise the infant may struggle resulting in the airway being extubated.

Complications from orotracheal intubation in neonates in the short term are infrequent and in the long term are small. Factors that are associated with increased complications include prematurity and low body weight, multiple intubation attempts, cuffed or uncuffed TTs that traumatize the loose columnar epithelium that lines the subglottic cricoid region, glottic and subglottic scaring, stenosis and injury, pharyngoesophageal injury and previous esophageal surgery, subglottic cyst, tracheal perforation, and dental injury [76–80]

Nasotracheal Intubation

Nasotracheal intubation is more challenging to perform than orotracheal intubation, especially in neonates. In the short term, nasotracheal offers some benefits over orotracheal intubation for certain procedures (e.g., with craniofacial anomalies [81]. cardiac surgery, posterior fossa neurosurgery, and for prolonged intubation in the intensive care in many institutions) although, in the long term, evidence suggests equipoise between the two TT approaches [82]. Nasally instilled 0.025% oxymetazoline (1 gtt/nostril) may be applied before intubation to reduce the risk of bleeding. The dose of the vasoconstrictor should be carefully calculated to avoid hypertension and reflex bradycardia progressing to cardiac arrest that have been reported after inadvertent overdoses of phenylephrine [83–86] and oxymetazoline [87, 88]. Hence, these agents should be used judiciously in neonates. Alternately, a red rubber catheter may be used in place of vasoconstrictors [89]. The catheter is passed through the nostril with the tip of the nasotracheal tube telescoped into the flange of the catheter, thereby obviating nosebleeds. Furthermore, if the neonate has limited oxygen reserves, it may be safer to perform an initial orotracheal intubation, then pass a second tube via the nose, and exchange the nasal for the oral tube during laryngoscopy. Although complications after nasotracheal intubation in neonates have been limited to anecdotal reports and in aggregate with older children, the specific complications that have been reported include traumatic damage to the cribriform plate, trachea and esophagus, false passages, nasal septal ulcers, blocked TTs [90–92].

The success rate of first attempt intubations by trainees and inexperienced staff is generally poor in neonates [93]. Initial studies of videolaryngoscopy compared with direct laryngoscopy in children failed to demonstrate a clear superiority of the videolaryngoscopy, although these were not randomized controlled trials. Recent randomized controlled trials, however, demonstrated that videolaryngoscopy improved the first attempt intubation rate and the time to intubation of neonatal airways with poor glottic views in part, due to the magnified view of the larynx as well as the guidance offered by the attending compared with direct laryngoscopy [94–96]. A recent randomized controlled trial of standard blade video laryngoscopy compared to standard blade direct laryngoscopy in infants with normal airways, demonstrated that video laryngoscopy improved first attempt success and reduced severe complications, particularly in smaller infants [97].

Selection of Tracheal Tubes

A variety of methods exist for determining the expected uncuffed TT diameter in children, including formulas based on age and height. However, in neonates, the diameter of the TT is determined empirically, based on the neonate's weight. For neonates <1.5 kg, a size 2.5 mm ID uncuffed tube is recommended, for those 1.6 to 3.5 kg, a size 3.0 mm ID uncuffed tube, and for those >3.5 kg, a 3.5 mm ID uncuffed tube. In the second half of the first year after birth, we use a 4.0 mm ID tube for infants ≥5 kg. The appropriate TT size for each neonate may need to be adjusted based on preexisting medical conditions (e.g., subglottic stenosis, Down syndrome) (Fig. 5.3a–c) and whether the tube is cuffed or uncuffed.

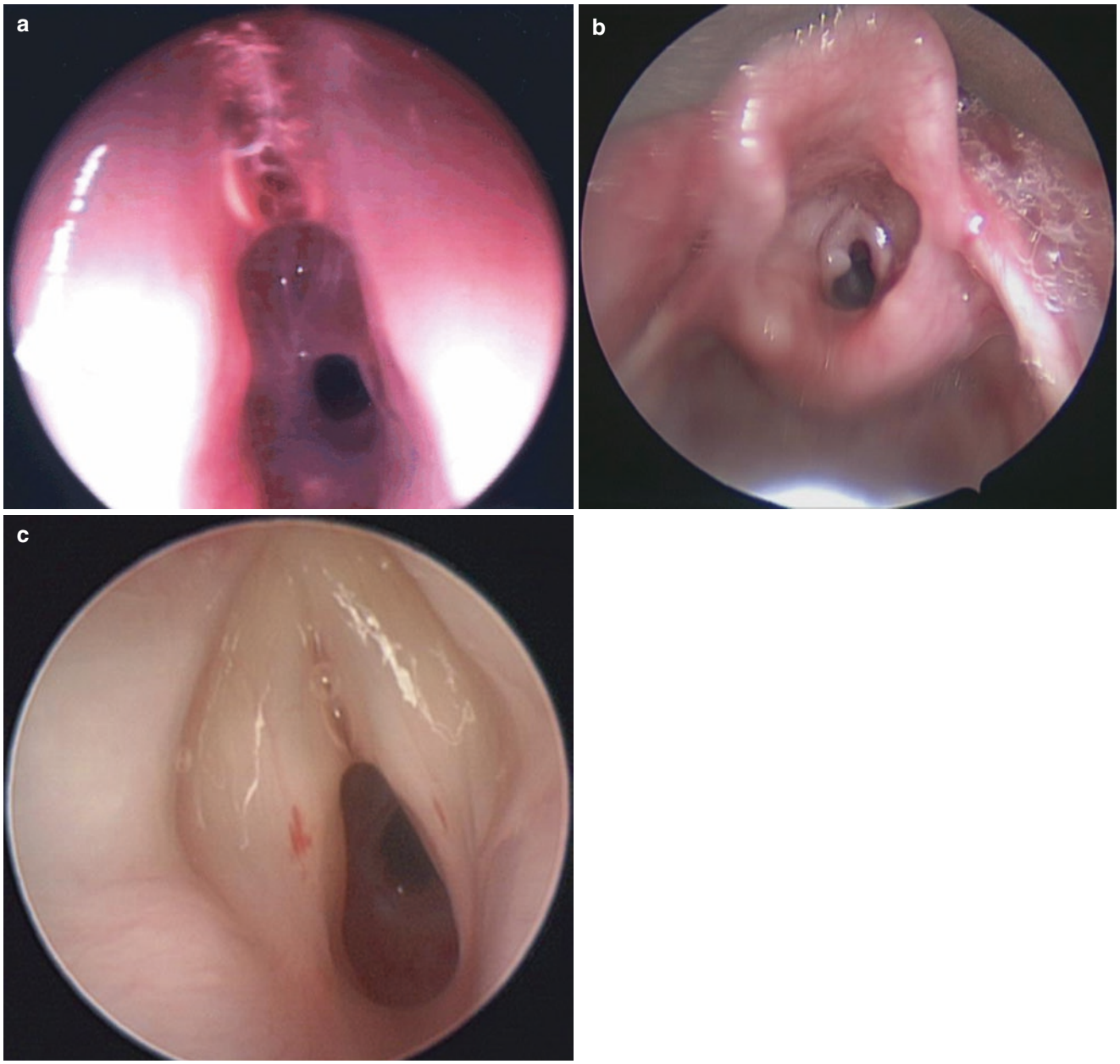

Fig. 5.3 (**a**) Bronchoscopic view of a subglottic web. (**b**) Bronchoscopic view of subglottic cysts. Courtesy of Dr. M. Benoit, Department of Otolaryngology, Strong Hospital, University of Rochester, NY. (**c**) Bronchoscopic view of subglottic stenosis after prolonged intubation in an ex-premature infant. Courtesy of Dr. M. Benoit, Department of Otolaryngology, Strong Hospital, University of Rochester, NY

Uncuffed Versus Cuffed Tracheal Tubes

Uncuffed TTs have traditionally been used in neonates due to the concern that a cuffed TT may cause subglottic injury. In the past, this was attributed to the walls of cuffed tubes being significantly thicker than those of uncuffed TTs and the fact that the cuffs were low compliance, exerting more pressure on the mucosa of the subglottic region for a given inflation volume. However, modern thin-walled cuffed TTs with high-volume, low-pressure cuffs have not been associated with an increased incidence of subglottic airway injury or an increased incidence of post-extubation stridor during general anesthesia in children and may reduce operating room pollution and anesthetic gas waste compared with uncuffed TTs [98–100]. In fact, in the pediatric intensive care unit, post-extubation stridor and significant long-term sequelae did not occur when cuffed TTs were used in infants and children for up to 6 days, although only 21 infants were allocated cuffed tubes [101]. In a recent study with the Microcuff® tube in infants and young children, 326 infants were studied with a 2.8% incidence of stridor [99]. The num-

ber of neonates in the latter study was not reported as a separate group. Recently, post-extubation stridor was reported in three neonates after the use of Microcuff® tubes, although it should be noted that these particular tubes used were NOT those recommended for their ages [102]. As of this writing, only one small retrospective study has compared the Microcuff and uncuffed TTs in neonates <3 kg [103]. There was no difference in complications and outcomes although only 23 infants were included in each group. *Readers should be cognizant of two additional issues regarding the Microcuff® tubes*: *1. the 3.0* (*not 3.5*) *mm ID Microcuff® tube is recommended for full-term neonates >3 kg up to 8 months of age*, *and 2. If the cuff of the Microcuff® tube is inflated*, *the cuff pressure should be monitored (maximum cuff pressure with these ETTs is 10 cm H_2O due to the elliptical shape of the cuff) throughout the anesthetic to preclude developing excessively high cuff pressures*. *The critical pressure that limits tracheal mucosal blood flow in the neonate is unknown*. Currently, neonatologists are reassessing their reticence to use cuffed TTs in neonates [104]. Long-term studies regarding the use of and complications from cuffed and uncuffed TTs in neonates have been forthcoming.

When a cuffed TT is used, the cuff inflation volume should be adjusted to achieve the desired leak pressure. The Microcuff® TT seals the airway at pressures that are less than traditional cuffed TTs. Accordingly, the time interval until the cuff pressure requires adjustment with the Microcuff® tube exceeds that with traditional polyvinylchloride TT [105]. Irrespective of the brand of TT used and whether nitrous oxide is used or not, it is prudent to either monitor the cuff pressure intermittently or deflate and reinflate the cuff periodically to preclude excessive cuff pressures and possible mucosal ischemia.

Cuffed TTs offer several potential advantages when compared with uncuffed TTs [104]. It seems intuitive that cuffed TTs should provide a better seal of the trachea to prevent macroaspiration than uncuffed tubes although this remains unproven (Fig. 5.4). The incidence of aspiration pneumonia with an uncuffed tube is exceedingly small and aspiration is known to occur even with cuffed tubes. They enable the use of small fresh gas flows (and associated economic advantages) and decrease operating room pollution. However, minimal fresh gas flows are also used with uncuffed tubes [100, 106]. In addition, cuffed TTs reduce the number of laryngoscopies to achieve a proper size tube and reduce the associated morbidity from multiple tube changes. The morbidity from reintubation is exceedingly small in experienced hands. Subglottic damage after intubation has been attributed, for the most part, to intubation with oversized TTs, prolonged intubation, and head movement [107]. Finally, two important and practical advantages of cuffed TTs should be appreciated. The first is to facilitate ventilation of lungs with reduced lung compliance such as in chronic lung disease. The second is for surgical procedures close to the airway to limit the escape of oxygen-enriched gases and thereby decrease the risk of fires by minimizing the oxygen concentration delivered and the use of suction Bovie devices.

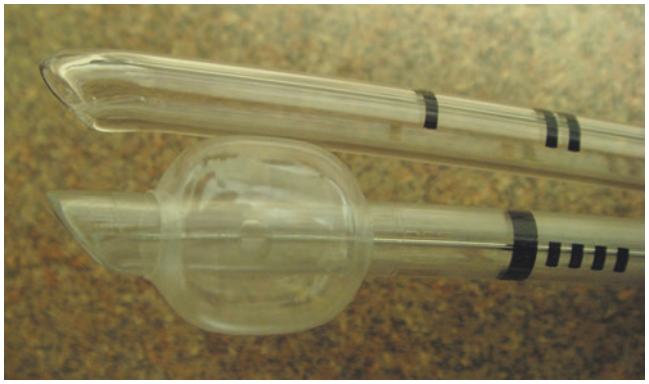

Fig. 5.4 An uncuffed and an inflated Microcuff® cuffed tracheal tube for comparison. Note the absence of the Murphy eye and the proximity of the cuff to the tip of the tube in the Microcuff® tube. The heavy *black line* on the Microcuff® tube corresponds with the vocal cord position in the neonate

Assessing Tracheal Tube Size

Before commencing tracheal intubation, it is important to prepare a selection of appropriately sized TTs. A tube with an outer diameter that will exert excessive pressure on the subglottic mucosa may cause mucosal ischemia and inflammation. In the short term, these events can lead to edema of the loose pseudostratified columnar epithelium that lines the subglottic cricoid region, the narrowest part of the subglottic trachea and the only circumferential cartilage in the trachea. This in turn may lead to stridor from the edematous narrowed airway that follows extubation. Since the flow of gas is turbulent (defined by a Reynold's number >2100) as far down the tracheobronchial tree as the fifth bronchial division, a narrowing of the cricoid ring, for example, by 50%, could increase the resistance to breathing by the radius to the fifth power or 32-fold (based on the Fanning equation for turubulent gas flow). With limited type I twitch fibers in the intercostal muscles and diaphragm, the extra work of breathing in such cases could lead to respiratory failure in the preterm (and term) neonate. In the long term, such inflammation may lead to scarring and, finally, subglottic stenosis.

The diameter of the uncuffed TT that is most appropriate for a neonate may be assessed using both the "air leak test" and by manually assessing the resistance to its passage through the subglottic region, which should be very small [108]. For the "air leak test," the tip of the tube is positioned mid-trachea and the adjustable pressure-limiting (APL) valve is closed. While the pressure within the breathing cir-

cuit increases, a stethoscope is positioned over the suprasternal notch. The pressure at which a leak is first heard is noted. Indirect evidence indicates that the leak pressure should be limited to 15–20 cm H_2O to minimize the risk of mucosal edema and tissue damage in adults [109]. Comparable evidence in neonates has not been forthcoming. When performing the "air leak test," it is important to avoid a slow and prolonged leak test as this might compromise the circulation, similar to that observed during a prolonged Valsalva maneuver.

If resistance is detected as the tube passes through the subglottic region, then a half-size smaller tube should be inserted. If the tube passes easily through the subglottis, it is important to auscultate for excessive gas leak to ensure that the tube is not too small for the larynx; otherwise, it is replaced with a tube a half-size larger. A leak test should then be performed to ensure that it is not too large.

Positioning the Tip

Ideally, the tip of the tracheal tube should be mid-tracheal level. A variety of formulae have been developed to predict the length of the TT to be inserted to achieve this depth. In neonates, a commonly used rule of thumb is the "123–789 rule," where a 1 kg baby should have the tube taped at approximately 7 cm at the maxillary alveolar ridge, a 2 kg baby should have the tube taped at 8 cm, and a 3 kg baby should have the tube taped at 9 cm for a mid-tracheal position. Even when such a formula is used, it is important to confirm optimal positioning. This can be initiated during laryngoscopy. When the cuff passes just beyond the vocal cords, or in the case of an uncuffed tube, when the tip passes 1–2 cm beyond the vocal cords, the centimeter marking on the tube at the level of the gums (or incisors) should be noted. Some prefer to advance the uncuffed tube until the breath sounds become unilateral. This identifies the level of the carina. The TT is then withdrawn 2–2.5 cm depending on the age of the child. The tip of the TT will then rest approximately midway between the vocal cords and the carina. Knowing the centimeter marking with this depth of insertion as well as the depth of the carina gives the anesthesiologist an idea of how much TT displacement can safely occur before an endobronchial intubation or tracheal extubation occurs. The distance between the glottis and the carina in full-term neonates is approximately 4–5 cm [110, 111]. Therefore, once the distance to the carina is found, the TT is pulled back approximately 2 cm to achieve a position that is mid-tracheal. A shortened tracheal length (i.e., a more cephalad bifurcation) is associated with certain medical conditions such as trisomy 21 [112] and myelomeningocele [113, 114]. These neonates are therefore at greater risk of accidental bronchial intubation, even when the TT is believed to be mid-tracheal. One should always be wary of a tracheal origin of the right upper lobe bronchus if a mild hemoglobin oxygen desaturation persists or air entry is diminished in the right upper chest and pull the TT back until the symptoms abate. In addition, a mid-tracheal tube position can be assessed by palpating the TT tip or the cuff in the suprasternal notch and by chest radiograph [115, 116].

Investigators have determined that the markings on the Microcuff® tube just proximal to the cuff more reliably ensure a properly positioned tube tip and cuff in the trachea than the cm markings at the lips (Fig. 5.4) [117]. Since the Microcuff® tube has no Murphy eye and does have a cuff, it is prudent to respect this recommendation and use the tube markings near the tip when positioning the TT rather than relying on the distance displayed at the lips.

It is important to recognize that flexion or extension of the head will affect the depth of intubation [118]. Flexion of the head advances the TT down the trachea, whereas extension withdraws the TT. While the distances involved are quite small in the neonate, it is wise to check the position of the tip of the TT after any manipulation of the head or body after intubation.

Rapid Sequence Intubation

The traditional rapid sequence induction (RSI) without ventilation is not usually feasible in neonates because they rapidly desaturate during apnea. This is a result of their relatively greater oxygen consumption, reduced FRC, and increased closing volumes compared with older children. Furthermore, it is difficult to pre-oxygenate the neonate because they often cry and move, preventing the application of a tight facemask. Therefore most pediatric anesthesiologists perform a "modified" RSI induction in neonates [119]. With this technique, the lungs are gently manually ventilated via a facemask using low airway pressures (<10–15 cm H_2O) as consciousness is lost. Once anesthetized and apneic, neonates and younger infants desaturate more rapidly than older children [120]. Thus continuous oxygen flow during laryngoscopy in neonates has been advocated via buccal oxygenation, nasal oxygenation or an oxyscope® laryngoscope blade [121, 122]. These approaches reduce the risk of a significant decrease in hemoglobin saturation. Furthermore, multiple intubation attempts during pyloromyotomy in neonates resulted in more hypoxemia than a single intubation attempt [123].

Controversy exists regarding the effectiveness of cricoid pressure to prevent regurgitation in patients after induction of anesthesia [124]. We do not recommend the routine application of cricoid pressure in neonates. Although a full discussion of this subject is beyond the scope of this chapter, what is known is that it is oftentimes difficult to palpate the cricoid ring in young infants [125], the force that is required

to occlude the lumen of the esophagus in neonates has not been established, that as little as 5 N may deform the airway in the infant [126], and that the esophagus is often displaced laterally, an effect that is far more prevalent in younger children than in adults [127]. In adults, the application of up to 50 Newtons force on the cricoid ring reduced the visibility of the glottis by 50% [128]. When 30 Newtons force was applied to the cricoid ring, the duration of fiber-optic intubation was prolonged compared with no cricoid pressure [129]. Although comparable data in neonates and children have not been forthcoming, it is reasonable to expect the effect of cricoid pressure on the visibility of the glottis opening to be limited even further. Supplementary maneuvers to minimize the risk of aspiration of gastric contents include emptying the stomach before induction of anesthesia, rapidly administering the induction agents, and rapidly securing the airway with a TT. In the event that cricoid pressure is applied, it should be maintained until pharmacologic paralysis is complete. In support of this practice, appropriately applied cricoid pressure has been shown to be effective in preventing gastric inflation during gentle bag-mask ventilation in anesthetized infants [130]. If the initial attempt at tracheal intubation fails while cricoid pressure continues to be applied, gentle facemask ventilation should be performed. If ventilation is difficult while cricoid pressure is applied, despite the use of adjunctive devices such as an oral or nasopharyngeal airway or an LMA, cricoid pressure should be lessened or released [131, 132]. The evidence that cricoid pressure prevents pulmonary regurgitation in this clinical setting remains unproven [133].

Managing the Difficult Airway

Epidemiologically, a difficult airway occurs more frequently in infants <1 year of age (with neonates comprising the second most common age group) than in older children [134]. Airway management in this population may be challenging; congenital and acquired airway difficulties [76, 106] and airway disorders due to a variety of conditions may cause difficult ventilation by facemask and/or difficult tracheal intubation. (Table 5.1).

The difficult airway in the neonate presents several unique challenges, in addition to those that exist in the older child. The small dimensions of the face, mandible, and neck present problems for maintaining a patent airway with the facemask and in the presence of the added difficult airway (e.g., small mandible, small mouth, large tongue) these challenges are magnified. Laryngoscopy and intubation may be very difficult due to the lack of uniformity of growth of the maxilla and mandible. Interestingly, such difficulties may change in magnitude and severity as the child grows and matures depending upon the underlying condition.

Table 5.1 Difficult airway in neonates

Difficult mask ventilation
Maxillary hypoplasia
Crouzon's syndrome
Apert's syndrome (acrocephalosyndactyly type I)
Pfeiffer's syndrome
Choanal atresia
Marshall–Smith syndrome
Rubinstein–Taybi syndrome
Possible difficult laryngoscopy/intubation
(a) *Micrognathia*
Pierre Robin sequence
Stickler syndrome
Smith–Lemli–Opitz syndrome
Treacher Collins syndrome
Goldenhar's syndrome; hemifacial microsomia
First arch syndrome; midfacial cleft
(b) *Possible micrognathia and other soft tissue facial anomalies*
Arthrogryposis trisomy 8
Trisomy 9
Trisomy 13 (Patau syndrome)
Trisomy 18 (Edwards syndrome)
CHARGE association
Cornelia de Lange syndrome
Velocardiofacial syndrome (Shprintzen syndrome)
Freeman–Sheldon syndrome (whistling face syndrome)
(c) *Macroglossia*
Beckwith-Wiedemann syndrome
Congenital hypothyroidism
Down syndrome
Cystic hygroma
Congenital lingual tumor/intraoral tumor
Mucopolysaccharidoses (Hurler, Hunter, Morquio, and Maroteaux–Lamy syndromes)[1]
Lipoid proteinosis trisomy 4p
Weaver syndrome
(d) *Intraoral/tracheal pathology*
Microstomia
Congenital temporomandibular joint dysfunction
Laryngeal/vallecular cyst, laryngeal web
Laryngotracheal cleft
Laryngeal/tracheal hemangiomas
Tracheal and subglottic stenosis
Other defects that may complicate the airway
Cervical spine immobility
Arthrogryposis
Emery–Dreifuss muscular dystrophy
Fibrodysplasia ossificans progressiva syndrome

[1]Data from Frawley G, Fuenzalida D, Donath S, Yaplito-Lee J, Peters H. A retrospective audit of anesthetic techniques and complications in children with mucopolysaccharidoses. Pediatr Anesth 2012: 22; 737–744

For example, superimposed on the difficulties posed by a normal neonatal airway, the flat face, maxillary hypoplasia, and small mouth of the neonate with Crouzon's disease and Apert's syndrome often leads to an obstructed airway during

facemask ventilation. In such instances, oropharyngeal airway or laryngeal mask airway may relieve the upper airway obstruction. However, direct laryngoscopy and orotracheal intubation in these cases is usually easy. As infants with these syndromes mature, mask anesthesia remains a challenge, whereas direct laryngoscopy remains easy.

Neonates with Pierre Robin sequence (Fig. 5.5a) [135], Treacher Collins syndrome (Fig. 5.5c), and Goldenhar's syndrome may also present challenging airways. Mask anesthesia may be difficult as the mandibular deformities render temporomandibular joint subluxation difficult (Fig. 5.5b) [136]. Pierre Robin sequence is defined by the triad of micrognathia, glossoptosis, and respiratory distress in the first 24–48 h after birth. Direct laryngoscopy may be particularly challenging in neonates with Pierre Robin sequence in part as a result of a short mandibular body length (Fig. 5.5b) [136]. However, the airway becomes easier to manage with age so that by 2 years, the mandible is often aligned with the maxilla [137]. In contrast, laryngoscopy in neonates with Treacher Collins syndrome is easier at birth and becomes progressively more difficult with increasing age, in some cases a tracheotomy is required by adolescence [137, 138]. This may be directly attributable to a shortened ascending ramus of the mandible [136]. In both Pierre Robin sequence

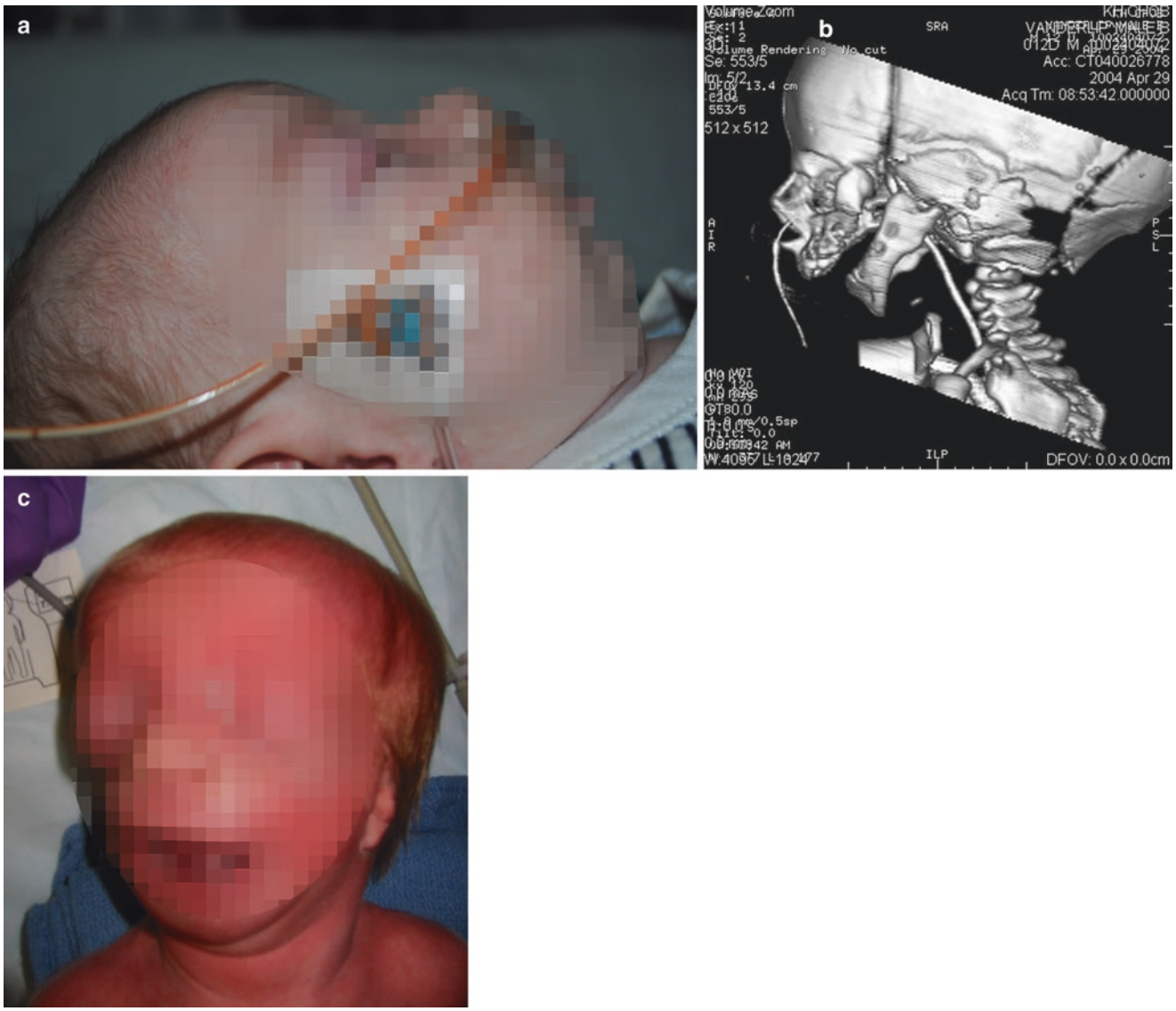

Fig. 5.5 (**a**) Lateral profile of a 3-week-old male with Pierre Robin sequence. Note the retrognathic chin, which will impair laryngoscopy and tracheal intubation. (**b**) A three-dimensional CT reconstruction of a neonate with Pierre Robin sequence. Note the hypoplastic mandibular body length and severely obtuse gonial angle (see text). Courtesy of Dr. J. Girotto, Department of Plastic Surgery, Strong Hospital, University of Rochester, NY. (**c**) Neonate with Treacher Collins syndrome. Note the small mandible, deformed ears, and teardrop eyelids, which are characteristic facial features of this syndrome

and Treacher Collins syndrome, the gonial angle (or the angle between the ascending ramus and body of the mandible) is significantly more obtuse than in unaffected neonates, which may contribute to difficult laryngoscopy exposure. The airway in neonates with Goldenhar's syndrome is split 50:50: half have airways are not difficult to manage, and half are exceedingly difficult to manage. Interestingly, the difficulty presented by the airway in this last syndrome does not change with age.

Neonates with disease of the larynx or trachea present a special challenge to the anesthesiologist. Mask ventilation may be difficult and tracheal intubation, if needed, requires careful consideration. The degree of airway obstruction and the dynamic changes that may occur with induction of anesthesia are often unknown and difficult to predict. Such patients include neonates with subglottic webs (Fig. 5.3a), hemangiomas, cysts (Fig. 5.3b), tumors, and laryngomalacia as well as those with subglottic stenosis from prior tracheal intubation (Fig. 5.3c) [139, 140].

Before embarking on an anesthetic for a child with a difficult airway, it is essential that the operating room and airway equipment are set up and immediately available (in the O.R.). Appropriate expert assistance (e.g., otolaryngologist) should be present before induction of anesthesia if a tracheotomy or rigid bronchoscopy (Fig. 5.6) is a possibility [141]. In elective cases, severely dysmorphic neonates and those with only a single means of accessing their airways (e.g., severe temporomandibular joint dysfunction that limits mouth opening and eliminates the ability to rescue ventilation with an LMA) should be evaluated by an otolaryngologist before induction of general anesthesia. This allows the otolaryngologist to assess the airway for alternate approaches to orotracheal intubation (such as rigid bronchoscopy or surgical tracheostomy) (Fig. 5.6) in the event that attempts at tracheal intubation fail. The availability of an otolaryngologist does not necessarily guarantee an expeditious airway rescue since the anatomical reasons that may lead to a failed intubation may also create difficulties for a tracheostomy [142].

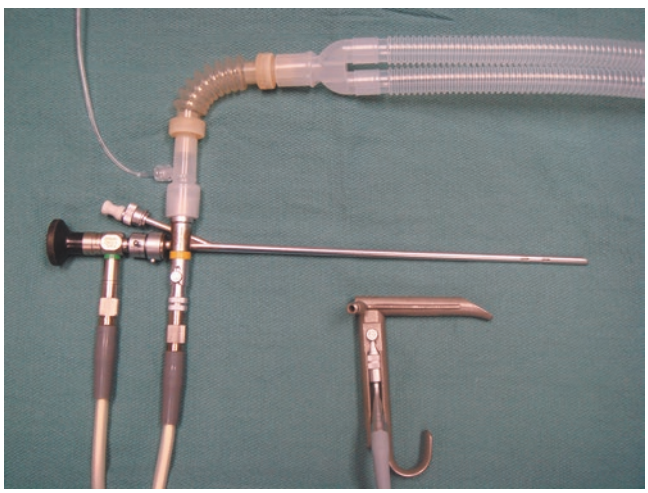

Fig. 5.6 A rigid bronchoscope with telescope and light source. Anesthesia breathing circuit with a flexible connector attached to the ventilation port of the bronchoscope. In the *lower right* of the photo, an anterior commissure laryngoscope is shown

The approach to the anticipated difficult neonatal airway is similar to that in older children. Although general anesthesia is the preferred approach to securing the airway in these infants, topical administration of local analgesia supplemented with sedation and awake tracheal intubation should also be considered as an alternative approach. During induction of general anesthesia, spontaneous ventilation is preferred as it makes it likely that ventilation will be maintained should the operators fail to secure the airway. However, spontaneous ventilation may be difficult to maintain in some neonates (particularly in the preterm and those with hypoplastic mandibles) because of the small dimensions of their upper airways, sensitivity to inhalational agents, and chest wall instability in addition to the defect at the root of the difficult airway. The decision to administer a muscle relaxant depends on the risk/benefit ratio of paralysis. This includes difficulty ventilating the lungs and a possible "cannot-intubate-cannot-ventilate" scenario developing, although the latter is exceedingly rare in neonates [143–145]. Induction of anesthesia must be carried out carefully, avoiding upper airway obstruction, and the consequent rapid desaturation.

Topical anesthesia applied to the airway combined with sedation has been used to blunt cardiorespiratory responses during laryngoscopy [1]. Alternately, sedation may be provided by midazolam and fentanyl, propofol, dexmedetomidine, or ketamine administered intravenously [65, 66, 69, 71, 72, 146–149] These approaches have all been used to secure the airway, although the responses were generally optimally only controlled when a muscle relaxant was coadministered.

Finally, an awake intubation may be necessary in order to secure the difficult airway, particularly in the absence of otolaryngology support or alternatives. The approach described earlier in this chapter to perform an awake orotracheal intubation should be followed closely in order to reliably and rapidly secure the airway. Once the airway is secured and expired carbon dioxide is identified, a bolus of intravenous propofol should be administered rapidly to induce general anesthesia.

The prior discussion has provided a detailed description of how to optimally use the Miller blade in neonates with a difficult airway. However, in some circumstances, the airway cannot be secured by direct laryngoscopy and other methods are required. These methods are described below.

Adjuncts such as an oropharyngeal airway or other supraglottic devices may be useful, particularly in the child with a dysmorphic face. Proper application of the jaw thrust [32] is usually salutary to re-establish an unobstructed upper airway. However, in the presence of a dysmorphic face or laryn-

gospasm, emergency intervention is required to establish an airway before hypoxemia and cardiac arrest occur. If time permits, an LMA has served as an effective bridge to tracheostomy in neonates in several difficult airway reports [137, 143, 150]. The appropriate size LMA should always be readily available in the event it is needed urgently. Alternatively, a video or optical technology may be required to visualize the glottic opening for tracheal intubation.

Several different video and optical technologies are available to manage difficult neonatal airways [45, 137]. In the past, much of this technology was simply scaled-down versions of adult designs [151], which were inappropriate for neonates [45]. This resulted in poor views of the airway and failed intubations [151]. There are several video laryngoscopes with pediatric-specific designs and a full range of pediatric sizes now available [151]. These include the Airtraq (Prodol, Vizcaya, Spain), Glidescope (Verathon Medical, Bothell, Washington, USA), McGrath (Aircraft Medical, Edinburgh, United Kingdom), Pentax AWS (Pentax, Tokyo, Japan), Storz C-MAC (Karl Storz, Tuttlingen, Germany), and the Trueview PCD (Truphatek International Ltd, Netanya, Israel).

Video laryngoscopes can be channeled (Airtraq, Pentax), or nonchanneled (Storz, GlideScope, Truview, McGrath). Channeled video laryngoscopes have a groove that houses the ETT and directs it toward the center of the viewed image [151]. Nonchanneled video laryngoscopes often require a stylet to successfully intubate [151].

The Storz Video laryngoscope (Fig. 5.7) and the GlideScope (Fig. 5.8) are two of the more commonly used video laryngoscopes that may be used to facilitate tracheal intubation in neonates [45, 152, 153]. The Storz video laryngoscope blade is available in Miller and Mac blade configurations, as small as a Miller 0 straight blade. A hyperangulated 60-degree "D-blade" is also available down to a size MAC 2 blade equivalent [45]. The Storz video laryngoscope has been used successfully in the delivery room, to facilitate tracheal intubation in neonates as small as 500 g [154]. The detailed view from the camera allows visual inspection of the airway in those suspected of having vocal cord dysfunction, laryngeal clefts (Fig. 5.9), and gastroesophageal reflux.

The GlideScope video laryngoscope has been successfully used in infants and neonates [155]. The redesigned GlideScope Cobalt is a Mac-style plastic blade that fits onto a video baton. It is available in all pediatric sizes and provides a clear, crisp view of the glottic opening, except in the most anatomically deformed neonatal airways. The GlideScope has undergone several modifications since it was first intro-

Fig. 5.8 Neonatal-sized GlideScope

Fig. 5.7 Neonatal-sized Storz video laryngoscope

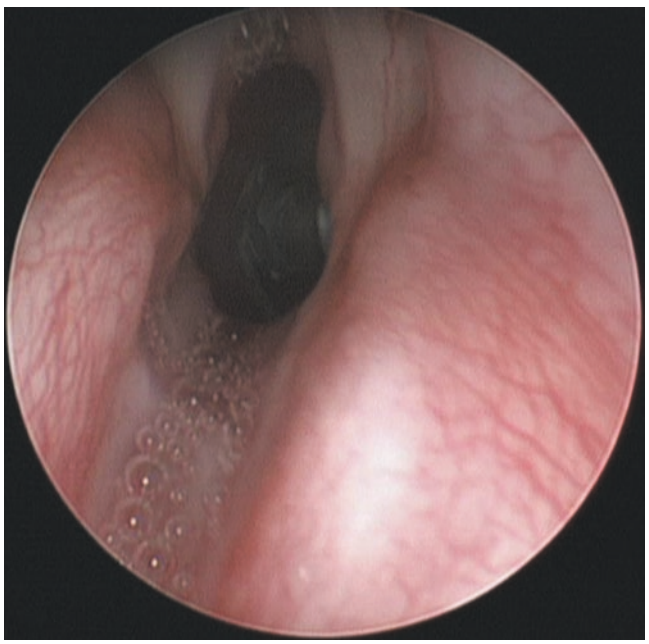

Fig. 5.9 Laryngeal cleft

duced, in 2000 [45]. The most commonly used variation, the AVL-S, is a single-use, digital device consisting of a "baton" (adult and pediatric version), and disposable, low profile, plastic blades called "stats." [45] The stat blades range in sizes for use in preterm neonates to adult size patients: stat size 0 (patients weighing <1.5 kg), size 1 (1.5–3.6 kg), size 2 (1.8–10 kg), and size 2.5 (10–28 kg) [45]. As is the case with any technology, there is a learning curve to navigate the TT into the glottic opening, while focusing on the video screen. Once this has been mastered, the device has a reliably excellent success rate in most neonates with craniofacial anomalies, provided the mouth opening is sufficient to accept the blade. The TT should always be visualized while it is advanced through the mouth to avoid tissue injury, especially when there is limited oropharyngeal space. The stat blade should be placed in the midline or the operators left in the pharynx to facilitate insertion of the tube. It is important to recall the glottic opening is more cephalad in the neonate. If the stat blade is inserted too close to the glottis, the ETT may be more difficult to maneuver into the trachea [45]. If the neonate proves to have microstomia, then the blade may have to be inserted slightly to the left of the midline, without sweeping the tongue [45]. Given the 60-degree curvature of the GlideScope stat, a styletted ETT must be used [156]. Several authors recommend using a C-shaped stylet following the curvature of the stat [155, 157, 158]. This curvature is similar to that of the GlideRite stylet [45]. Other authors recommend the use of a hockey-stick-shaped stylet [159]; however, in younger children, this may make maneuvering the styletted ETT more challenging and require additional maneuvers such as the use of Magill forceps or the BURP [160].

Given the special features of the neonatal airway discussed earlier, difficulty may be encountered passing the ETT beyond the vocal cords despite having an excellent view of the glottic opening [151]. If the glottic opening is too close to the tip of the airway device, the leading tip of the ETT may hang up on the right arytenoid, preventing the tube from advancing through the vocal cords [45] or possibly avulsing the right arytenoid if excess pressure is applied. Obtaining a Cormack and Lehane grade 2 view by slightly withdrawing or reducing the anterior lift of the device provides a better trajectory for passing the ETT [151]. Another common scenario is difficulty passing the ETT in neonates, because the tip impacted the anterior commissure of the vocal cords or the subglottic trachea. In this situation, "reverse loading" the ETT onto the stylet can be helpful [151, 161]. Typically, a styletted ETT has the murphy eye located to the right of the laryngoscopist due to the natural curvature of the tube. Reverse loading is accomplished by rotating the ETT so that the murphy eye is to the left of the operator [151]. This reverses the orientation of the ETT curve and directs it more in line with the axis of the trachea reducing "hang up" in the anterior wall of the trachea [151]. Alternately, simply withdraw the stylet 1–2 cm and rotate the ETT 90° clockwise so that the bevel faces upward. After either of these maneuvers, the ETT may be advanced, with the bevel glancing off the anterior commissure or tracheal wall and then continue beyond the vocal cords.

The Airtraq optical laryngoscope (Prodol, Vizcaya, Spain) is a single-use curved laryngoscope that uses mirrors and prisms to transmit the image from the tip of the device to a viewfinder (Fig. 5.10) [153]. It can be used in neonates, with sizes ranging up from neonatal size 0 [45]. It has a conduit for the TT along its side that directs the TT toward the glottic opening as it is advanced. The Airtraq has been used successfully in managing the difficult airway in the neonate, although there are no controlled randomized trials in neonates [153, 162–166]. Despite the built-in channel, one publication described two cases (one neonate and one infant) in which a full glottic view was obtained, and yet, difficulty was encountered when directing the tube into the trachea. The authors attributed the failures to the bulk of the device that limited its maneuverability [167]. Others have had success utilizing a gum elastic bougie to facilitate placement of the TT when the standard approach failed [168].

The Pentax AWS is a portable vide laryngoscope designed to be uniquely used as an indirect laryngoscope [45]. The device has a small video screen attached to the device as well as the capability to view the video output on an external monitor. The Pentax is inserted into the mouth in the midline, and once the glottis is visualized, an ETT is passed through a channel embedded in the blade [45]. The device is available in neonatal to adult sizes. The Truview EVO2 (Truphatek, Netanya, Israel) incorporates a prismatic lens in an angulated rigid blade (Fig. 5.11) [153]. It has a side port for oxygen insufflation during intubation. When the Truview was compared with the Miller blade in neonates, the former provided improved Cormack-Lehane views and a clinically insignificant increase in the time to tracheal intubation [169]. Caution should be exercised when insufflating oxygen at excessive flows (i.e., Bonfils recommends <3 L per minute of oxygen flow) through these intubation devices as subcutaneous emphysema has been reported [170].

The McGrath video laryngoscope is a portable device with disposable blade sheaths similar to the standard MAC blade with blade sizes ranging from MAC size 2–4 [45]. A size 1 MAC blade has been developed but is not currently available in the USA [171].

When using any of the video-assisted intubation devices described above (except for the Airtraq), the selected TT should be prepared with a lightly lubricated stylet before laryngoscopy. An anterior curve matching the blade angle of the selected device facilitates successful placement of the tube. Laryngoscopy is performed by introducing the blade in the midline or to the right of the tongue, and airway structures are progressively visualized until the blade tip is placed either in the vallecula or under the epiglottis. With the tip

Fig. 5.10 Neonatal-sized Airtraq optical laryngoscope

Fig. 5.11 Neonatal-sized Truview EVO2 (courtesy of Dan White, Truphatek, Inc.)

positioned in the vallecula and the glossoepiglottic ligament engaged, the scope elevates the epiglottis and exposes the glottic opening in most infants. On occasion, the epiglottis obstructs the camera view because of its length in neonates and infants. In this case, the epiglottis should be gently lifted with the blade to expose the glottic inlet. After a satisfactory view has been obtained, the TT is passed along the shaft of the blade (unlike the lateral insertion typical with standard direct laryngoscopy). This insertion technique guarantees that the TT will come into the view of the video camera as it is advanced and reduces the risk of soft tissue injury.

Whether tracheal intubation is easier, faster, or more successful on the first attempt with a videolaryngoscope in neonates and infants compared with direct laryngoscope has been a subject of some debate. In a meta-analysis of video and direct laryngoscopy in infants and children, a distillation of 27 trials concluded that time to intubation is similar with both devices in infants, success was similar on first attempt to intubation with both, although videolaryngoscopy reduced the number of traumatic airway events [172]. However, when videolaryngoscopy was used in neonates with normal airways during resuscitation, the success rate for tracheal intubation was improved and intubation time was reduced in the hands of inexperienced staff compared with no benefit for either in the hands of more experienced staff [173]. When the success rate for tracheal intubation using videolaryngoscopy with standard blades (e.g., Miller or Macintosh Glidescopes, Storz CMAC, and others) was compared with nonstandard blades (e.g., Airtraq, UE Scope, King VL, and others) in the Paediatric Difficult Intubation Registry, videolaryngoscope with conventional blades resulted in a significantly greater success rate for intubation in the difficult airway in neonates and infants <5 kg compared with nonconventional blades [174].

A recent randomized controlled trial of standard blade video laryngoscopy compared to standard blade direct laryngoscopy in infants with normal airways demonstrated that video laryngoscopy improved first attempt success and reduced severe complications, particularly in smaller infants. There were also fewer esophageal intubations in the video laryngoscopy group.*

The lighted stylet remains a viable option for intubating the neonate with a difficult airway [175, 176]. A stylet for neonatal use can easily be fashioned from readily available equipment in the operating room. A single fiber-optic light bundle (20 g Fiberoptic Endoilluminator, Cat No. MVS1011, Storz, St. Louis, MO, USA) can be inserted into the chosen TT alongside a rigid stylet, and the fiber-optic bundle is then connected to a rheostat-controlled fiber-optic light source (Fig. 5.12) [176]. Transillumination of light in the neck is used to guide the placement of the TT; however, because of the relative lack of subcutaneous fat in neonatal patients, changes in light intensity with esophageal placement may not be readily appreciated. Thus, lighted stylet intubation in the neonate requires an element of feel, and observing the transilluminated light continuously. A brief disappearance and reappearance of the transilluminated light suggests esophageal placement. The visualization of a cone of light in the caudad direction suggests correct tracheal positioning.

Optical stylets combine the rigidity of the lighted stylet with fiber optics to allow direct visualization during intubation. The Shikani Optical Stylet (SOS; Fig. 5.13) and the Bonfils fiber-optic laryngoscope (Fig. 5.14) represent two designs with neonatal applications. The SOS is malleable, whereas the Bonfils is rigid with a fixed curve of 40°. Both are limited by the presence of secretions but have been successfully used in neonates. Optical stylets can be combined with the anterior commissure laryngoscope or a standard laryngoscope to facilitate intubation; the laryngoscope displaces soft tissue and provides an unobstructed path for the stylet to be maneuvered [177]. Some authors have reported less success with the Bonfils when compared with standard laryngoscopy [178], whereas others have questioned its utility [179, 180]. The Bonfils has, however, been used successfully with a 2.5 mm ETT in a small-for-gestational-age neonate in whom direct laryngoscopy failed [181].

Fig. 5.12 A single fiber-optic light bundle is attached to a rheostat-controlled light source and placed inside a styleted endotracheal tube to form a "homegrown" lighted stylet

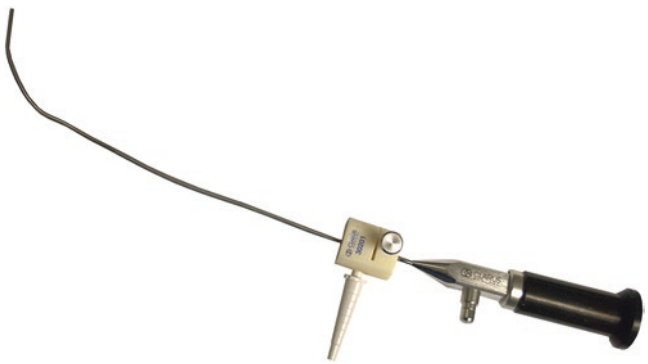

Fig. 5.13 Neonatal-sized Shikani Optical Stylet

Fig. 5.14 Neonatal-sized Bonfils fiber-optic laryngoscope

The flexible fiber-optic bronchoscope has been widely used for decades now to pass an ETT into the airway in the neonate with a difficult airway when direct laryngoscopy failed. A channel has been incorporated in neonatal size bronchoscopes, which may be used to remove secretions [182]. If difficulty is encountered with the oral and nasal approaches, fiber-optic intubation through an LMA should be considered. This technique has been used successfully for tracheal intubation in neonates. A correctly positioned LMA simplifies intubation with the flexible fiber-optic bronchoscope and allows continuous ventilation via a swivel adapter [183–189]. With the increasing use of cuffed tubes in children, practitioners should be aware that most neonatal LMAs will not allow the passage of cuffed TTs without some modifications to the pilot balloon cuff [190]. The exception to this is the air-Q intubating LMA (Mercury Medical, Clearwater, FL), which readily accepts the pilot balloon of the cuffed tube [191, 192]. In neonates with severe upper airway obstruction, the LMA can be placed in the awake infant and followed by induction of general anesthesia and fiber-optic intubation [193–196]. Placement of a modified nasal airway provides an alternative option for oxygenating the neonate during intubation. In small infants with the potential for life-threatening upper airway obstruction during induction of general anesthesia (e.g., large cystic hygroma), moderate sedation may be administered using small, incremental doses of ketamine and midazolam after the application of topical anesthesia [197] to provide suitable conditions while maintaining spontaneous respiration during the laryngoscopy and tracheal intubation.

In neonates, multiple attempts at tracheal intubation can cause upper airway edema that becomes so severe that it

compromises ventilation. In such a case, an otolaryngologist should be consulted to evaluate the neonate for a tracheostomy as the airway must be secured.

In a CICV situation, needle cricothyroidotomy has been traditionally recommended to establish an airway in older children and adults [198]. However, this is NOT a practical option in neonates, because the neonatal cricothyroid membrane is slit-like with overlap of the cricoid and thyroid cartilages [199]. The neonatal cricothyroid membrane is too soft and too small for surgical cricothyroidotomy to be performed (measuring 2.61 mm in length and 3.03 mm in width in neonatal cadavers) [200]. Attempts to pass a tracheal or tracheostomy tube could result in laryngeal fracture or severe airway injury. The lack of a laryngeal prominence in the neonate combined with a more cephalad glottic position makes localizing the membrane in the neonate very difficult, much more difficult than in the adult. In a recent case of CICV in a 3-year-old child, emergency tracheotomy was attempted after multiple failed attempts at cricothyrodectomy [201]. To date, there are no reports of needle cricothyrotomy performed in a neonate of any size. The Quicktrach baby™ (VBM Medizintechnik GmbH, Sulz am Neckar, Germany) is a percutaneous cricothyrotomy device that was designed and introduced for use in neonates/infants. In a comparative study using dead rabbits (whose size was comparable to neonates), the Quicktrach baby™ was successful in zero of 13 attempts whereas the cannula tracheotomy was successful in 60% [202]. To repeat, we do NOT endorse percutaneous cricothyrotomies in neonates at this time.

The difficult neonatal airway represents one of the most challenging clinical scenarios for the pediatric anesthesiologist. If the difficult airway is anticipated, then appropriate planning must take place. However, in those rare instances in which the difficult airway is unanticipated, prior familiarity with a difficult pediatric airway algorithm is essential [141] Consistent success requires adequate preparation, maintenance of skill with indirect visualization devices, and assembling the appropriate personnel when assistance may be required.

Managing the Airway in the Ex Utero Intrapartum Treatment (EXIT) Procedure (See Chap. 14)

Rare conditions may occasionally result in compromised and potentially life-threatening neonatal airway immediately after birth. These conditions include (but are not limited to) congenital cystic hygroma of the neck, congenital high airway obstruction syndrome (CHAOS) caused by obstruction at the level of the larynx or trachea, and cervical teratoma (see Fig. 5.15) or other tumors of the face, mouth, and neck.

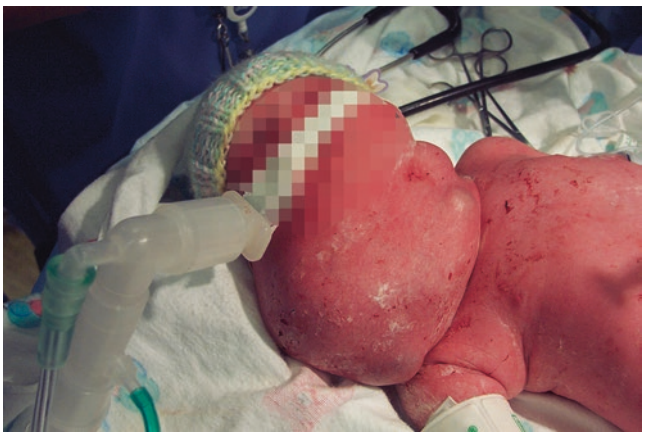

Fig. 5.15 Cervical teratoma in a neonate with an orotracheal tube.

If a suspected challenging airway is diagnosed antenatally, the time of delivery may be scheduled to ensure that an ex-utero intrapartum treatment (EXIT) procedure and the EXIT team is present at the delivery to support the neonate until the airway has been established [203–205]. The EXIT procedure is performed with a partially delivered fetus, while the uteroplacental circulation remains intact. EXIT procedures permit direct laryngoscopy/bronchoscopy and tracheal intubation, tracheostomy, or tumor resection depending on the defect present. Figure 5.16a, b show a neonate and CT scan of that neonate who presented antenatally with a hamartoma of the hard palate. An EXIT procedure was planned, although orotracheal intubation was successfully performed by an anesthesiologist upon delivery of the fetus. The benign tumor was subsequently resected. In some centers, airway management is performed entirely by the surgical team. Once the neonate's airway is secured using a TT or surgical airway (depending on the size and location of the obstructing lesion), the placental cord may be ligated and severed.

Fetal anesthetic management consists of transplacental transfer of volatile anesthetics (via the mother who receives general endotracheal anesthesia) and an intramuscular injection of atropine, fentanyl, and vecuronium into the fetus, once it is exposed via a uterine incision. Total muscle paralysis is critical to prevent the fetus from taking a breath, which would cause a switch from fetal to transitional circulatory pattern.

EXIT procedures may also be performed for resection of congenital pulmonary masses and cannulation for extracorporeal membrane oxygenator (ECMO) support for select congenital cardiac conditions. The original indication for the EXIT procedure was to remove a tracheal plug that was placed during mid-gestation in an attempt to promote pulmonary development in fetuses with congenital diaphragmatic hernia [206].

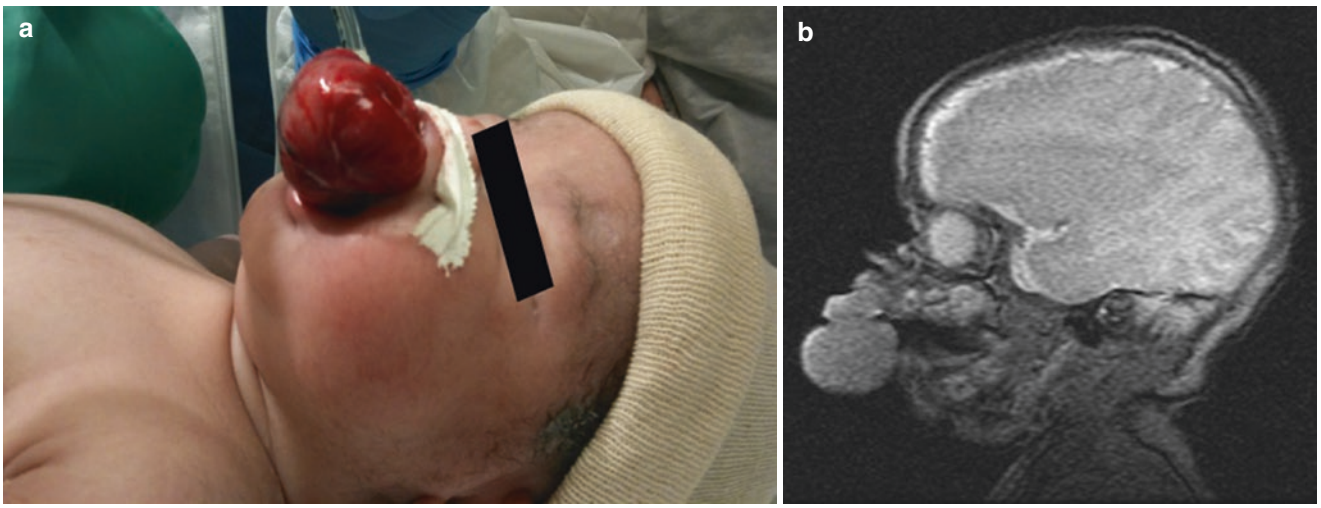

Fig. 5.16 (**a**) Neonate with a hamartoma of the hard palate. (**b**) CT scan of the neonate demonstrating a clear and patent nasopharyngeal airway

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Neonatal Ventilation Strategies and Their Practical Application

6

Adam Balogh and Walid Habre

Recently, large cohort studies demonstrated that ventilation issues increased perioperative morbidity and mortality in neonates [1, 2]. Inadequate ventilation, manifested as either hypo- or hyperventilation, had respiratory and systemic consequences that may have contributed to morbidity and mortality [3, 4]. Strategies were developed to improve lung ventilation with a "protective" and "open-lung" strategy to optimize functional residual capacity (FRC) and prevent ventilation-induced lung injury (VILI) and bronchopulmonary dysplasia (BPD). Clinicians have since become aware of the potential harm of excessive hyperventilation in neonates because of large tidal volumes (Vt) that overdistend alveoli, increase wall shear stress, and liberate pro-inflammatory cytokines, which are the main features of the so-called VILI [5, 6]. Moreover, the resultant hypocapnia that results from extreme hyperventilation induces cerebral vasoconstriction and may promote the development of cystic periventricular leukomalacia [7]. Alternately, suboptimal Vt may result in poor gas exchange and hypercapnia that potentially increases the risk of intraventricular hemorrhage (IVH) [8]. Thus, several different ventilation modes are now available based on the application of volume guarantee modes to optimize tidal volume and meet the ventilation requirements of the neonate according to the physiological characteristics of the respiratory system and the fluctuations in lung compliance. Despite these new developments in ventilation, there is no evidence of the superiority of any one of these new ventilation strategies in terms of neonatal pulmonary and neurodevelopmental outcomes. Recently, there has been growing interest in the use of noninvasive ventilation in neonates, although evidence of its beneficial effects on both the lungs and the brain has been elusive. Whatever ventilation strategy is used, clinicians should be reminded that real-time pulmonary monitoring is essential to adapt the ventilation strategy to sudden changes in the mechanical properties of the lung that often occur during surgery. This chapter reviews the pulmonary indices and function in the neonate, describes the different ventilation modes available, and highlights the importance of using a protective and open-lung ventilation strategy.

Respiratory System

Three specific physiological characteristics distinguish the respiratory system in the neonate. First, the chest wall, which is made up of the intercostal muscles and ribs, is highly compliant in the neonate because the ribs are horizontally oriented and cartilaginous (non-ossified), giving the infant's thorax a cylindrical shape of the rather than the elliptical shape seen in older children. Moreover, the effectiveness of the intercostal muscles to augment and support the chest wall and minimize chest wall distortion during inspiration is limited, contributing less to the developing tidal volume in neonates compared with older children. The main muscle that is responsible to develop the tidal volume in neonates is the diaphragm. However, in neonates, the diaphragm has less muscle mass, fewer high-endurance Type 1 twitch fibers, and inserts more horizontally than in older children [9]. Thus, in neonates with respiratory distress and increased oxygen requirements, when the diaphragm contracts, the lower rib cage moves inwards rather than downwards as seen in older children. In aggregate, the chest wall characteristics limit the ability of the neonate to increase alveolar ventilation efficiently and effectively in the face of stress. Thus, the neonate will be predisposed to early fatigue [10]. In the preterm neonate, these effects are even more extreme with a very low percentage of slow-twitch, high oxidative fibers that present

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as poorly developed ventilatory muscles, even less mature than those in term neonates [9].

The second important feature in the neonate that limits their ability to respond to increased ventilatory demand is the presence of the so-called "stiff lung." This latter term relates to the increased static elastic recoil of the lung. The elastic recoil is determined by the elastic fibers within the lung and by the surface tension force generated at the air–liquid interface within the alveoli [11]. Surfactant reduces surface tension and maintains the patency of the terminal airways, independent of the alveolar diameter [12]. The high elastin/collagen ratio in neonates predisposes the lungs to collapse. Furthermore, the very compliant chest wall presents little resistance to hold the lungs open, resulting in a much smaller resting volume at end-expiration. The forces that favor the collapse of alveoli are opposed by those that prevent the lung from collapsing. The net effect of these opposing forces corresponds to the functional residual capacity (FRC) and represents the resting volume of the respiratory system. Consequently, even after externally delivered, effective lung surfactant, the FRC in the neonate is relatively small, and even smaller in the preterm neonate. In the latter age group, respiratory distress syndrome arises from a deficiency in surfactant, which causes the terminal airways to collapse. These changes may lead to atelectasis, loss of lung volume, and hypoxemia. This phenomenon is further exaggerated in the preterm neonate because collateral airflow does not occur at the level of the bronchoalveoli because the terminal airways are immature and alveolarization is disturbed [13, 14].

Finally, the neonatal respiratory system is challenged by the increased airway resistance that arises in the upper airways and larger conducting airways of the lungs. The resistance of the upper airways can be substantial in neonates, as the resistance to airflow in the narrow conducting airways down to the fifth bronchial division is inversely proportional to the fifth power of the reduction in the radius of the lumen as presented by the Fanning equation for turbulent flow (Reynold's number >2100) (e.g., if the radius of the upper airway decreases by 50%, the resistance to gas flow increases by 32-fold). The radius of the airway may decrease substantially due to thickened mucous membranes arising from an inflammatory disorder, infection, or secretions. Thus, the radius of the airway is the most important determinant of the resistance of the upper airway. However, beyond the fifth bronchial division, the rapid increase in the cross-sectional area of the airways decreases the velocity of gas flow and resistance to flow. With the decrease in gas flow, the Reynold's number decreases to <1800 and the flow becomes laminar. In laminar flow, the resistance is inversely proportional to the fourth power of the decrease in radius (Poiseuille's equation for laminar flow). Furthermore, airway resistance decreases as the child grows in height [15, 16]. In neonates, airway resistance may also increase from airway closure and the loss in lung volume. One should be aware that when looking at the total respiratory system resistance, the tracheal tube combined with the resistance from the forces generated by the viscoelastic component of the lung account for more than two-thirds of the total resistance of the airway. In neonates, the use of tracheal tubes with small diameters increase the respiratory resistance, and the relatively high elastic recoil of the lung may further exacerbate the resistive component of the respiratory system [15]. Thus, when ventilating the lungs in a neonate, the peak pressure applied should overcome both the frictional forces that result from the airway resistances as well as those from both the tissue elastic recoil and the chest compliance. Many clinical conditions observed in neonates may alter the effectiveness of ventilation, jeopardizing our ability to maintain normocapnia and adequate oxygenation. Accordingly, positive pressure ventilation may become challenging in the presence of decreased lung compliance such as that seen with surfactant deficiency or congenital diaphragmatic hernia, which result in loss of lung volume. Other congenital or acquired diseases (tracheomalacia, bronchial infection, and inflammation) may increase resistance to airflow and require specific ventilation modes to avoid very high intratracheal pressures that may contribute to VILI.

Key Points

- The specificity of the ventilatory muscles and the increased airway resistance contribute to respiratory fatigue in neonates.
- The viscoelastic feature of the neonatal lung is the main determinant for optimal ventilation.
- The surfactant plays a key role for alveolar stability and prevention of ventilation heterogeneity.

Ventilation Modes

A better knowledge of the neonatal respiratory pathophysiology as well as the advances obtained in ventilator technology have led to various complex ventilation modes, the usefulness of which has not yet been adequately proved primarily because of the lack of randomized trials in the neonates. Although the varied ventilation modes used routinely in the neonatal intensive care unit (NICU) have confusing terminology, many are simply not available on the anesthesia ventilators to deliver inhalation agents during surgery. However, the current ventilation modes can be distinguished based on whether they are volumetric (e.g., flow generator), barometric (the pressure generator), or a combination of both pressure and flow generators (dual modes). New ventilators in anesthetic workstations allow the child to trigger the onset of the ventilator cycle, which provides partially controlled or support ventilation modes.

Pressure-Controlled Ventilation

This mode is the most popular ventilation strategy in neonates and is often recommended for use in clinical practice. The basic and most frequently applied mode in NICU is the time-cycled, pressure-limited ventilation (also called intermittent positive-pressure ventilation (IPPV)), and is also available with most anesthesia ventilators where it is termed pressure-controlled ventilation (PCV). The decelerating flow and the limited and constant inspiratory pressure that characterize this ventilation mode explain the reduced peak inspiratory pressure, which is accompanied by the reduced tracheal and alveolar pressures. This mode compensates for a potential leak around uncuffed tracheal tubes with leaks, still routinely used during anesthesia in neonates [17]. The combination of decelerating flow and constant airway pressure over time facilitates the equilibration of tracheal and alveolar pressures. Evidence suggests this mode improves ventilation distribution, and thereby gas exchange [18]. However, when applying PCV, three main factors are integral to determining the tidal volume: (i) the pressure gradient between the maximum inspiratory set pressure (peak inspiratory pressure (PIP)) and the positive end-expiratory pressure (PEEP), which defines the driving pressure, (ii) the inspiratory time (T_i) that may depend and/or determine the ratio between the inspiratory and expiratory times as well as the respiration rate, and (iii) the time constant to equilibrate the airways and alveoli pressures, which is a function of the total respiratory system compliance and resistance. Therefore, when setting the PCV mode, the operator should (i) select the T_i and expiratory times (T_e) to determine the respiration rate close to the child's physiological rate, (ii) adjust the peak inspiratory pressure (PIP) and the PEEP, (iii) select the inspiratory flow rate, and (iv) select the inspired concentration of oxygen. Although ventilating with a short or extended T_i does not affect the incidence of chronic pulmonary disease (CPD) in neonates, a short T_i may decrease the risk of an air leak and mortality [19]. The normal physiological T_i in neonates is between 0.35 and 0.5 s, which dictates the initial setting for T_i with a higher T_e. This helps to establish the initial respiration rate. However, under anesthesia both T_i and PEEP can be increased in order to increase the mean airway pressure and thus tidal volume and to recruit alveoli [20]. At the same time, the higher T_i may also jeopardize venous return and cardiac output. Alternately, shortening T_i during weaning may help to synchronize the neonate's respiration with the ventilator and is more advantageous in neonates. To overcome this limitation, synchronized ventilation with the neonate triggering the onset of ventilation is currently the common mode used in NICUs. Among the different triggering techniques that have been developed, flow triggering via a flow sensor interposed between the tracheal tube and the ventilator's connection is the most sensitive [21] and is therefore routinely used in clinical practice. Synchronized intermittent mandatory ventilation (SIMV) pressure control mode and assist-control (AC) modes have been introduced in the intensive care settings to synchronize the respiratory rate with the child's breathing (SIMV) or by assisting each breath using positive-pressure ventilation, but with a "control" of a minimum number of ventilator cycles (AC). Nonetheless, if the child breathes very frequently, the ventilator assists all of the triggered breaths by applying the initial T_i, which will decrease the T_e and may lead to air trapping by reducing the time required to adequately exhale. This risk is also observed when using pressure support ventilation (PSV), a mode that has been introduced on almost all new anesthesia ventilators. In the PSV mode, the child's breathing effort and the changes in the airflow together initiate and terminate the ventilator assistance. An important feature of this mode is that the child determines the T_i. Depending on the type of ventilator, expiration begins when the inspiratory flow level decreases to between 10 and 25% of the maximum inspiratory flow [22]. This mode is of interest to anesthesiologists. This ventilator mode has been used in older children to reduce the work of breathing (WOB) associated with spontaneous breathing and to counteract the greater resistance due to small tracheal tubes. Because of the greater risk of patient–ventilator asynchrony in the ill neonate whose respiration rate is very rapid, PSV may increase oxygen consumption and generate possible ineffective ventilatory efforts. Another novel technique called proportional assist ventilation (PAV) has been developed to prevent such phenomena, offering to further reduce the WOB. In this mode, the neonate controls the rate of lung inflation and thus the peak inspiratory pressure, which is proportional to the neonate's efforts [23]. Since the pressure applied depends on the inspiratory flow generated by the neonate, this ventilation mode assumes that the neonate is not hypopneic and that there is no leak around the tracheal tube [20]. However, this ventilation mode, which is not available in anesthesia workstations, is known as the airway pressure release ventilation (APRV). This mode is based on the combination of a large continuous positive airway pressure and brief releases of the pressure, which are short enough to generate auto-positive end-expiratory pressure [24]. This mode generates large intratracheal pressures, but is advantageous when the neonate is breathing spontaneously throughout the APRV cycle. Although its effectiveness has not been elucidated [25], APRV has been associated with better cardiopulmonary interactions and improved lung perfusion in infants after cardiac surgery [26]. Of more widespread interest is the neurally adjusted ventilator assist (NAVA), which relies on the child's respiratory control and diaphragmatic activity [27]. The inspiratory effort is detected via bipolar electrodes mounted on a nasogastric feeding tube and positioned at the level of the diaphragm. The level of ventilatory support is then proportional to the inspiratory effort. Even

though this mode is unaffected by a leak around the tracheal tube, its utility is still not well-defined in neonates, especially in preterm infants with immature control of the ventilation. A very recent prospective crossover study demonstrated that NAVA is associated with improved patient–ventilator synchrony and a reduced peak airway pressure in comparison with PSV [28]. More recently, new modes of ventilation that were based on individualized variable ventilation experimentally promoted lung protection while providing adequate gas exchange both in normal and injured lungs [29, 30]. These new ventilation modalities based on the physiological variable ventilation in neonates could be beneficial during prolonged ventilation in the absence of a respiratory drive.

Volume-Controlled Ventilation

The major disadvantage of pressure-limited ventilation is that the tidal volume (Vt) varies, because of changes in the compliance of the lung and resistance of the airways, which occur frequently in neonates during both anesthesia and surgery. As a consequence, some anesthesiologists continue to advocate for volume-controlled ventilation (VCV), a strategy that is based on the traditional delivery of a fixed predetermined Vt at a preestablished rate. This mode does not, however, take into account the maximum inspiratory pressure needed to deliver the desired Vt. Furthermore, high tracheal pressures may be encountered during surgery, especially when the lung compliance decreases and/or airway resistance increases to deliver the predetermined Vt. These high driving pressures may be limited either by setting the pressure pop-off valve or by determining the level of T_i in order to limit excessive peak inspiratory pressures during mechanical ventilation of low compliant lungs. Nonetheless, this mode of ventilation is deceptively misleading, particularly in neonates, as the preset Vt is not delivered to the lungs since this mode does not compensate for the tidal volume lost to the compression of the gas within the ventilator circuit, the compliance of the breathing circuit and the leak around the uncuffed tracheal tubes. It is imperative that ventilation is monitored using a capnogram and oxygenation using an oximeter.

Volume-Targeted Ventilation

The increasing awareness of the usefulness of direct control of the PIP and the benefit of ventilation with a small, constant Vt led clinicians to develop dual-mode ventilation strategies to guarantee Vt with a limited pressure [31]. Several ventilators and ventilation modes have since been developed and are routinely used in the intensive care to deliver a target or guaranteed Vt with an adjustable high-pressure limit to autoregulate the maximum inspiratory pressure (within the maximum limit set) or the T_i to guarantee the target Vt. These modes are known as volume-targeted ventilation modes and include all of the modes that guarantee Vt by adjusting the inflating pressure in response to the exhaled Vt, which is compared with the target Vt [32]. There is evidence that volume-targeted ventilation reduces adverse outcomes including severe intraventricular hemorrhage (Grade 3 or 4), periventricular leukomalacia, and CPD when ventilating the lungs of preterm neonates compared with pressure-limited ventilation [33–35]. New anesthetic workstations now include ventilators with these modes, although these findings have not been documented during anesthesia and surgery, despite the theoretical advantage to deliver the Vt at a reduced intratracheal pressure, particularly when compliance and resistance vary during surgery.

Among the new ventilation modes developed, the volume guarantee (VG) ventilation mode is a pressure-limited, volume-targeted time or flow-cycled ventilator that has garnered the interest of clinicians. The driving pressure for this mode is based on the difference between the exhaled and predetermined Vts. The software analyzes each breath individually to maintain constant Vts. This mode can be combined with other standard ventilation modes often used in neonates such as SIMV, AC, or PSV. In addition to setting the maximum PIP to limit lung injury, both the desired Vt (exhaled Vt) and T_i are set, which determine the duration of insufflation. These ventilator characteristics are particularly appealing in preterm neonates who are weaned from spontaneous respiration since the inspiratory pressure is adjusted in real-time [31]. Other anesthesia workstations use the pressure-regulated volume control (PRVC) mode in which the gas flow rate is adjusted to generate an inspiratory pressure sufficient to deliver the targeted Vt [36]. Thus, this ventilation mode shares many similarities with pressure control modes in terms of the pressure and flow patterns but delivers the target Vt by adjusting the PIP based on the compliance of the lung. One study demonstrated that this ventilation mode is very effective in very low birth weight (VLBW) preterm infants as both the duration of mechanical ventilation and hemodynamic instability are less than those that occur with other ventilation modes [37, 38]. Furthermore, this mode is associated with lower peak intratracheal pressures and its impact on hemodynamics is less than with other modes [39]. When this mode is combined with other ventilator options that allow infants to breathe spontaneously with pressure support, it is called “auto mode,” which is currently built into some anesthesia workstations. To date, there have been no studies that document the advantages of this ventilation mode in neonates.

High-Frequency Ventilation

High-frequency ventilation (HFV) rapidly became a strategic and favorite ventilation mode in neonates with chronic and severe lung disease as ventilation is ensured by applying small tidal volumes at a MAP (mean airway pressure) that is higher than with conventional ventilation. This strategy is very effective in infants with severe respiratory failure since HFV improves the gas exchange by optimizing the lung volume while ventilating at lower proximal airway pressures, thereby avoiding lung damage [40]. The principle upon which HFV is based on the natural "resonant" frequency of the lung and that less pressure is required to move the gas into and out of the lungs at its resonant frequency, which is around 10 Hz (1 Hz = 60 bpm) in neonates and even greater in preterm infants. HFV improves the gas exchange by enhancing both the convection and the diffusion of respiratory gases. Different ventilators delivering HFV are available without evidence that one type of HFV ventilator is superior to another. The first ventilation modality was high-frequency jet ventilation (HFJV), a technique that has become well-established in anesthesia. This mode delivers quick bursts of gas (with very short T_i) at very high frequency (up to 600/min) combined with a constant gas flow that determines the level of PEEP. This technique required a specific tracheal tube but failed to prove its effectiveness in clinical practice as the neurological and respiratory outcomes in neonates were conflicting [41–43]. Another modality that used HFV is known as high-frequency flow interruption (HFFI), consisting of a continuous gas flow, which is delivered by a high-pressure gas source that is interrupted at a high frequency (up to 20 Hz) [44]. This technique also failed to become widely adopted as it offered no advantages in pulmonary outcomes and yielded a greater incidence of air leaks in preterm babies compared with traditional ventilation modes [45, 46]. The most frequently used ventilation mode currently is high-frequency oscillatory ventilation (HFOV). This mode is based on the presence of an electromagnetically driven piston or vibrating diaphragms that generate biphasic pressure waveforms at very high frequencies (up to 15 Hz). Thus, HFOV has both an active inspiratory phase and an active expiratory phase (by inducing a negative proximal airway pressure during exhalation). When using HFOV it is important to adjust the I/E ratio to avoid gas trapping that may occur as a result of the active exhalation part [22]. HFOV provides very small oscillatory tidal volumes that are superimposed on an adjustable MAP. HFOV offers a particular advantage when a large tidal volume strategy is required to maintain the FRC as HFOV maintains FRC with a smaller MAP compared with other modes of ventilation. Nevertheless, a recent meta-analysis failed to demonstrate any benefit of HFOV over conventional ventilation modes when it is used as a primary or rescue mode to ventilate infants with acute pulmonary dysfunction [47]. The incidence of chronic lung disease in preterm babies may be less if the lungs are ventilated with HFOV but the evidence is weak [47]. Nonetheless, HFOV may still have a great clinical benefit in the operating room, particularly to ventilate low compliant lungs in neonates with congenital diaphragmatic hernia or severe respiratory distress.

Continuous Positive Airway Pressure and Noninvasive Ventilation

Many neonates may benefit from noninvasive respiratory support that applies continuous positive airway pressure (CPAP) and/or the delivery of noninvasive ventilation (NIV). Nasal CPAP maintains the FRC by recruiting and maintaining a patent airway and inflated lungs [48]. It also decreases the WOB and reduces the frequency of apnea of prematurity [49]. Therefore, nasal CPAP has become a standard ventilation strategy to support the lungs in recently extubated preterm infants, as an alternative to tracheal intubation and ventilation, to support those experiencing significant apnea of prematurity and for those with respiratory distress soon after birth. Some newer systems also provide a phasic positive increase in pressure (pressure support or pressure-controlled) in addition to the CPAP and can be synchronized (SNIMV, synchronized nasal intermittent mandatory ventilation) or not (NIMV). During the past decade, the use of NIV in neonatal intensive care units for acute respiratory failure has been expanding and the factors that predict the successful use of NIV have recently been identified [50]. While meta-analyses have failed to demonstrate the benefit of NIV in the presence of respiratory distress syndrome [51], its ability to prevent extubation failure in neonates is well established [52]. Accordingly, the use of NIV to protect against the risk of reintubation during the first 72 h is the current evidence-based indication for NIV in neonates [48]. For this purpose, NIV is started after the minimal PEEP level is set to ~6 cmH_2O and the PIP to 10–12 cmH_2O.

CPAP can be delivered by one of two techniques: (i) A continuous flow and a device that varies the exhalation either by modifying the expiratory orifice size or by immersing the distal end into a water reservoir to a specific level, the depth of which defines the level of CPAP. This latter is known as bubble CPAP—the bubbles creating pressure oscillations that are transmitted to the airway opening. It has been suggested that this phenomenon may improve gas exchange by facilitating diffusion [53]. (ii) A variable flow that allows changes in the level of CPAP using nasal prongs, which redirect the exhaled gas out of the expiratory limb. The WOB with the variable-flow CPAP is less than that with the bubble CPAP [54]. Another system that is based on the variable-flow setting is the bi-level CPAP or BiPAP. BiPAP allows the

child to trigger the inspiratory phase and to breathe between two levels of positive pressure, with some systems including an abdominal wall sensor to synchronize inspiration with the child's efforts. The BiPAP system may be better at improving oxygenation and ventilation than the CPAP system in low birth weight (LBW) infants [55].

The application and successful use of CPAP and NIV rely on the airway interfaces and their ability to guarantee comfort and optimize the delivery of pressure to the airway. Of all the interfaces that provide CPAP, the bi-nasal prongs are superior [56]. Although bi-nasal prongs are associated with a greater incidence of nasal trauma in infants [22], leaks remain a major concern in NIV. Such leaks may reduce alveolar ventilation, impair child–ventilator synchrony, and increase nasal resistance.

Nasal High-Flow Oxygenation

In the last decade, nasal high-flow oxygenation (NHFO) has gained widespread popularity in several populations, particularly in neonates, to improve oxygenation and/or as an alternative to noninvasive ventilation. This method is based on the delivery of a mixture of air and oxygen via a nasal cannula at a high gas flow, matching or exceeding the child's peak inspiratory flow. Compared with conventional low-flow (2 L/min) nasal cannulae, NHFO delivers greater gas flow rates, at 1–4 L/kg/min in neonates. Such large gas flows necessitate the prior heating and humidification of the gas mixture since the delivery of a cold, dry gas would desiccate the mucosa of the nasal cavity and the lower airways, leading to trauma and airway edema, as well as impairing mucociliary flow. The net result is to retain secretions [57]. Thus, this technique is also referred to as heated, humidified nasal high-flow, and accordingly, current devices integrate a heater–humidifier to deliver a gas mixture at a temperature of 37 °C saturated with water. The choice of the prongs (made of soft silicone) is of importance in neonates as a sufficient leak (20–50% of the nares' internal diameter) should be allowed around to cannulae to both facilitate expiration as well as to prevent the accumulation of excessive end-expiratory pressures generated by the continuous flow [58].

Several mechanisms have been proposed to explain the improved oxygenation with NHFO. First, since the gas flows delivered by the NHFO match or exceed the peak inspiratory flow, and the nasopharyngeal dead space is constantly washed out by the gas mixture, room air entrainment and CO_2 rebreathing are reduced. Consequently, the partial pressure of oxygen in the nasopharyngeal space is closer to the set FiO_2 during NHFO compared with low-flow oxygenation, resulting in a greater diffusion gradient for oxygen between the upper airway and the alveoli. Secondly, NHFO creates positive airway pressure that increases airway patency and end-expiratory lung volume [59]. This pressure correlates linearly with the flow [58, 60, 61] and depends on the child's weight as well as the size of the leak around the prongs [62]. Unlike CPAP or noninvasive ventilation, NHFO generates pressures that vary during both inspiration and expiration. Since airway pressures depend on both the direction and the magnitude of the ventilation flow relative to the delivered flow, pressures are minimized at end-inspiration and maximized at mid-expiration, with end-expiratory pressures decrease in between the two readings [63]. In preterm infants, gas flows of 2–8 L/min delivered by three different NHFO devices resulted in end-expiratory pharyngeal pressures of 2–6 cmH_2O, with a mean increase of 0.5 cmH_2O for each 1 L/min increase over 2 L/min [62, 64], albeit with large variance. Although there is no clear consensus, mouth opening did not affect the pharyngeal pressures in neonates and infants, unlike in adults [60, 62, 65, 66].

Finally, irrespective of the gas flows being between 2 and 8 L/min, NHFO decreased the WOB as evidenced by transcutaneous diaphragmatic electromyography and respiratory inductance plethysmography [67, 68]. Decreased airway resistance due to the splinting effect of positive pressure, decreased minute ventilation due to dead space washout, and decreased metabolic demand due to the heating and humidification are all plausible mechanisms that individually or in aggregate decrease the WOB.

In spontaneously breathing neonates [66] and preterm infants [62], NHFO improves oxygenation and elimination of CO_2, although it failed to prevent hypercapnia in apneic children [69, 70]. Nonetheless, during the past decade, NHFO has been increasingly used for apneic oxygenation during intubation and airway procedures to prevent or delay oxygen desaturation [69–72]. In neonates and infants aged 0–6 months, NHFO increased the mean time to desaturate to an SpO_2 of 92% from 109 s to 196 s [70]. The improved oxygenation during NHFO is due to pharyngeal dead space washout, greater achievable FiO_2, airway splinting effect, and maintenance of the FRC. However, the failure to augment CO_2 elimination may be explained in part by the structural properties of the neonatal airways. A computer simulation suggested that a key mechanism that clears CO_2 during NHFO is via cardiogenic oscillations augmenting alveolar ventilation [73]. However, in the apneic infant and child, cardiac oscillations are not augmented because airway resistance is increased and this might explain why NHFO failed to clear CO_2 from the lungs [74]. This peculiarity may explain the similarity in oxygenation during apnea after administering 100% oxygen at 2 L/kg/min via NHFO and that via traditional low-flow cannulae at 0.2 L/kg/min [70].

In summary, NHFO may be considered an effective strategy to oxygenate the infant during airway procedures by prolonging the time available to intubate the trachea, particularly in the neonate, those with a difficult intubation [17] and those

with limited oxygen reserves [70, 75]. It is essential to recognize that despite oxygenating the child, NHFO incompletely clears CO_2 during apnea. Alternately, maintaining oxygenation via a traditional low-flow cannula is a suitable and cost-effective method to routinely implement in clinical practice.

Key Points

- There is a shift from controlled mechanical ventilation to combined modes with spontaneous ventilation to improve alveolar ventilation and cardiopulmonary interactions.
- The pressure-regulated volume control mode meets the specific characteristics of neonatal respiratory physiology.
- There is still no evidence for the advantage of one given mode over the other as clinical trials in neonates are sparse with large inhomogeneity.

Application of Ventilation Modes in the Operating Theatre

Despite the great advances in the development of new anesthetic ventilators, which include a variety of modes of ventilation widely used in the operating room and intensive care setting, the benefits of these modes of ventilation during general anesthesia to improve clinical outcomes have not been forthcoming. In neonates, these ventilation modes contribute to "lung protective ventilation" by optimizing the distribution of ventilation in the presence of alveolar instability. Alveolar instability refers to the presence of both collapsed and overdistended alveoli in the lungs. The repetitive alveoli recruitment and collapse generated by positive pressure ventilation with each breath may cause excessive dynamic shear stress on the alveolar walls, while overdistensing adjacent alveoli produces a dynamic strain with each breath. As a consequence, a new concept was recently developed that promotes "specific tidal volume," which is determined by the driving pressure determined by the inspiratory pressure over the PEEP level set on the ventilator. The goal is to optimize gas exchange while decreasing lung stress and strain. Thus, the most appropriate ventilation mode would be the one that maintains the smallest driving pressure as possible to meet the "lung protective ventilation" concept.

Therefore, the traditional mandatory VCV strategy is far from the ideal strategy to ventilate the lungs in the neonate because it connotes a constant flow that generates large driving pressures and fails to account for the compressible volume of the breathing circuit and the potential gas leak around uncuffed tracheal tubes. The constant flow characterizing the VCV mode induces large PIPs with less time for equilibration between the airway pressure (Paw) and the alveolar pressure (Palv), known as the time-constant. Moreover, the compressible volume is an important issue in the neonate and it is important to understand whether the ventilator corrects for this compressible volume in the case of a fixed Vt setting. Most modern ventilators available in anesthesia currently correct for the compressible volume when the ventilator is checked during the machine check. If there is a change of circuits between infants, it is important to recheck the compressible volume as the neonate's Vt may be of a similar order of magnitude as the compressible volume. It is also important to ensure that the tidal volumes displayed on the workstation monitor are accurate by performing the pre-use anesthesia workstation testing (which compensates for circuit compliance) with the circuit tubing in either the compressed or expanded state, depending on how the circuit will be used during anesthesia [76]. For a ventilator that predates software that corrects for compressible volume or limits compensation if the pressure exceeds 30 cmH_2O [77], it is essential to account for the compressible volume when setting the Vt. For example, if the compressible volume reaches 1 mL/cmH_2O, and the delivered Vt is 7 mL/kg in a 4 kg neonate, the ventilator may generate a PIP of 25 cmH_2O during ventilation, yielding a compressible volume of 25 mL. The preset Vt should be adjusted to almost 13 mL/kg since 50% or more may be lost due to the compressible volume (not taking into account the dead space and the potential leak). Thus, the use of the VCV mode requires that the overpressure valve be set to protect the lung from any dangerous increase in peak inspiratory pressure that may result from changes in lung compliance during the surgery. In neonates, particularly those with less compliant lungs, we believe that PCV is the preferred T_e mode of ventilation in neonates.

The decelerating flow pattern that characterizes the PCV mode offers a limited and constant inspiratory pressure with a plateau pressure that is reached much faster, but at a lower PIP and thus driving pressure than VCV. This mode improves the distribution of ventilation and decreases the intrapulmonary shunt, thereby improving oxygenation. Furthermore, the PCV mode compensates for the presence of a gas leak around tracheal tubes. Although PCV better satisfies the criteria required by the protective-ventilation strategy, Vt will fluctuate in this mode, particularly if lung compliance decreases or respiratory resistance increases during surgery. During PCV, Vt depends on three components: (i) the time constant, (ii) the pressure gradient between the maximal set peak pressure and the PEEP level, and (iii) T_i, which is determined by the respiration rate and the *I*/*E* ratio. The time constant is characterized by the mechanical properties of the respiratory system, which include the total respiratory system compliance (Crs) and resistance (Rrs). Application of the time constant concept to the inspiratory phase implies that T_i is set to allow sufficient time to equilibrate the pres-

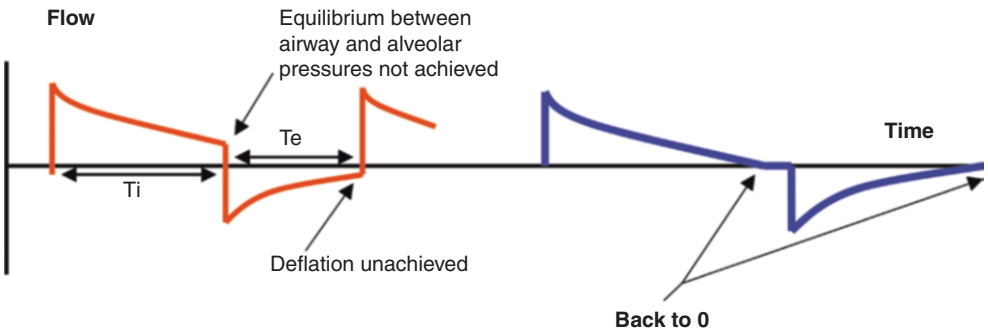

Fig. 6.1 Flow vs time curve demonstrating the "time constant concept" with decelerating flows. T_i should be of sufficient duration to permit the inspiratory flow to return to 0. Similarly, T_e should be of sufficient duration to preclude intrinsic PEEP. T_i Inspiratory time, T_e Expiratory time, *PEEP* Positive end-expiratory pressure

sures between the airways and alveoli. Accordingly, if Rrs increases and/or Crs decreases, the time to equilibration will increase. Further, it is important to allow sufficient time to complete deflation, as the expiratory flow has an exponential decelerating profile that can take up to 3 to 4 time constants of the respiratory system to completely deflate (see Fig. 6.1).

Finally, it is important to note that anesthetic ventilators that are currently available vary in the maximum insufflation flow they can generate. Thus, the Vt generated by a given pressure level may vary from one ventilator to another [78]. Considering T_i is short and the respiratory rate is rapid in neonates, it is important to note that the physiological T_i does not exceed 0.5 s. However, in an anesthetized neonate, who is paralyzed with a muscle relaxant, one may exceed this T_i to recruit alveoli. At the same time, increasing the T_i may also impact hemodynamic variables and lead to asynchrony if the PSV mode is selected. Therefore, the initial ventilator settings in PCV mode should include the pressure gradient established with a PEEP of 5 cmH_2O and a positive inspiratory pressure over PEEP of 10 cmH_2O. The respiration rate will be determined by initially selecting a T_i up to 0.6 s. The choice of both the T_i and the pressure gradient will depend on the compliance and the resistance of the respiratory system and the blood gas analysis. It is also important to consider T_e, particularly in neonates with obstructive lung disease, such as bronchopulmonary dysplasia, where the expiratory time constant should permit sufficient time to exhale to minimize auto-PEEP and hyperinflation.

PSV mode has become popular in routine practice in pediatric anesthesia as it maintains diaphragmatic activity during general anesthesia, which decreases ventilation–perfusion mismatch. New ventilators include a flow trigger that is very sensitive to minimal variations in flow rate (similar to those observed with intensive care ventilators) and can therefore be applied in neonates since a minimal WOB is required to initiate an inspiratory effort [79]. The pressure support is based on a decelerating flow, which generates a fixed insufflation pressure; thus, Vt may vary with the neonate's inspiratory efforts, the level of pressure support, and the mechanical characteristics of the lung as well. Currently, few modern anesthetic ventilators have cycling adaptation (transition from inspiration and expiration). In the case of ventilators with fixed cycling, insufflation will stop when the flow is less than 25% of the maximum inspiratory flow. This limitation may have a negative impact on the neonate with obstructive disease for which cycling should occur later [80]. Although studies using the PSV mode in neonates have not been forthcoming, this mode can be applied during anesthesia in clinical practice to compensate for the increase in the WOB, which is particularly great in neonates. For instance, the application of pressure support of 5 cmH_2O in addition to PEEP at induction will maintain patent airways, thus offsetting the WOB and optimizing the gas exchange during inhalation inductions. During the maintenance phase of anesthesia, more pressure support may be necessary (up to 10 cmH_2O) to overcome the resistance from the tracheal tube and the anesthesia circuit, as well as to guarantee an optimal Vt for gas exchange [81]. After anesthesia, the PSV mode allows for a smoother recovery, emergence, and weaning from the ventilator. In all cases, it is important to set a minimum respiration rate to deliver breaths in a pressure control mode even during an apnea. In such a case, PCV adapts T_i to avoid asynchrony with the ventilator that may increase the WOB. Lastly, some anesthetic ventilators allow changes in the pressure slope (the time to achieve pressure support). By increasing this time (and thereby decreasing the pressure slope), we can limit the auto-trigger activated by the cardiac activity, which is frequently observed in neonates at low trigger threshold [82]. To avoid this phenomenon, it is also possible to increase the trigger threshold with the risk of increasing the WOB.

Recently, the PRVC mode with auto mode (auto-flow) was introduced in new anesthetic ventilators in the operating theatre. VCV with a decelerating flow in combination with synchronization with a pressure support of the spontaneous ventilation offers the advantages of pressure modes with a

guaranteed minimum Vt. Theoretically, this mode overcomes the inconvenience of both PCV and VCV and may offer an enormous advantage in anesthetized neonates, particularly when lung compliance decreases abruptly during surgery (i.e., laparoscopy, or abdominal or thoracic surgery). To determine the initial guaranteed volume, the child's lungs should initially be managed using pressure control and extract the tidal volume that ensures adequate alveolar ventilation. Thereafter, the determined tidal volume can be considered as the targeted tidal volume in PRVC mode while adapting the ventilator setting according to PCV mode and by applying a maximum inspiratory pressure of 30 cmH_2O to protect the lungs from overpressure. Nonetheless, no data have been forthcoming regarding the use of this ventilation mode in the operating theatre, particularly in neonates and hence although this mode meets the physiological characteristics of the lung during surgery, its usehas remained anecdotal and based on the experience of different clinicians.

Key Points

- *Alveolar instability* promotes ventilation heterogeneity with excessive shear stress and enhancement of dynamic strain at each breath.
- Ventilation modes with decelerating flows provide a low driving pressure and thus exert less lung stress and strain.
- Allowing spontaneous ventilation with pressure support as soon as possible improves ventilation homogeneity and cardiorespiratory hemodynamic interactions.

Ventilation Strategy in the Operating Theatre

Maintaining adequate ventilation during sedation or anesthesia is of particular importance in neonates, who are vulnerable to hypoxemia. Inadequate bag and mask ventilation during induction of anesthesia may result in insufficient alveolar ventilation, hypoxemia, hypercapnia, and gastric inflation and regurgitation of gastric contents with subsequent pulmonary aspiration. Furthermore, the accumulation of air within the stomach may further compromise respiratory function and gas exchange in neonates whose functional residual capacity is less than its closing volume. While the use of an accessory circuit such as a modified T-piece breathing system (i.e., Jackson Rees) continues to be advocated as the best system to ensure both adequate ventilation and maintenance of FRC [83, 84], it is important to monitor airway pressure during manual ventilation to avoid both excessive peak inflation pressure and gastric air insufflation. The development of low resistance circle systems rendered their use in routine practice popular [85, 86], although they may be less effective in applying a continuous positive airway pressure (CPAP) at end-expiration to maintain upper airway patency and FRC. In this context, applying gentle mask ventilation with CPAP to maintain a mean airway pressure around 5–10 cmH_2O becomes an increasingly popular ventilation strategy at induction of anesthesia, even in the presence of a full stomach to avoid airway collapse and to ensure adequate oxygenation [87, 88]. Alternatively, using PSV at induction of anesthesia will ensure an adequate CPAP level to maintain the FRC and a low-pressure support to optimize alveolar ventilation. This so-called controlled induction technique meets the criteria for an "open-lung strategy," which should be considered at all stages when ventilating a neonate's lungs in the operating theatre.

The open-lung strategy primarily addresses concerns about atelectasis and the resultant ventilation inhomogeneity observed during general anesthesia, which can significantly impair pulmonary gas exchange. First, the physiological characteristics of the chest wall (large compliance) and the lung (increased static elastic recoil pressure) in neonates promote airway closure and a decrease in FRC. The decreased ventilation associated with general anesthetics and inactivation of the intercostal muscle activity associated with the cranial shift of the diaphragm are also responsible, in part, for the lungs collapsing and atelectasis formation. The latter is enhanced by the resorption of alveolar gas when an excessive FiO_2 is used. Thus, this "open-lung strategy" requires that recruitment maneuvers should be regularly performed, particularly after the loss of positive end-expiratory level (at zero PEEP level). Such recruitment can be achieved by applying a vital capacity maneuver (or twice the Vt, but limiting the maximum inspiratory pressure to 30 cmH_2O in normal lungs) after induction, after disconnection and suction, and thereafter every 30 min during the anesthetic procedure [89]. However, a minimum PEEP level of 5 cmH_2O is required to maintain the recruitment of the distal airways [90], while high concentrations of oxygen should be avoided as tolerated. Nonetheless, an increased PEEP may be required in the presence of poorly compliant and atelectatic lungs to maintain adequate alveolar recruitment.

Beyond this open-lung strategy, it is crucial to apply "protective ventilation" in an attempt to protect against VILI, which has been associated with an increase in lung stress and strain [91]. Ventilation with small Vt at optimal FRC is therefore essential in the operating theatre as well. Optimizing the level of PEEP will increase the lung volume, while adapting T_i and T_e will guarantee adequate lung inflation and deflation, respectively, especially if T_i/T_e is adjustable based on estimations of the time constants. This "protective ventilation" strategy should account for the continuous changes in respiratory compliance of the neonate undergoing surgery and the ventilation inhomogeneity.

This ventilation strategy may lead to mild hypercapnia, 6–6.5 kPa (61–67 cmH_2O), which is regarded as safe in the absence of high intracerebral pressure and pulmonary hypertension. Furthermore, mild hypercapnia improves both the cerebral oxygen saturation and the subcutaneous tissue oxygenation [92]. Fetal hemoglobin has a greater affinity for oxygen compared with adult hemoglobin, thus explaining the leftward shift of the oxyhemoglobin dissociation curve in the neonate and the resultant reduced P50. Further reduction in the P50 may occur with hyperventilation (Bohr effect), thereby further decreasing tissue oxygen delivery [93]. Moreover, hyperventilation and/or the application of large tidal volumes may lead to hypocapnia and thus, cerebral vasoconstriction, a major risk factor that predisposes to cerebral ischemia and possible neurocognitive impairment in young infants [4].

Therefore, in an attempt to meet the physiological requirements stated above, it is advisable to always consider the pressure-regulated volume control mode. This mode delivers a constant tidal volume with the smallest inspiratory flow and driving pressure and prevents perturbations in the carbon dioxide tension. Studies demonstrated a greater incidence of cerebral insults in infants with extreme carbon dioxide, partial pressures less than 4.6 kPa (47 cmH_2O) or greater than 6.6 kPa (67 cmH_2O) [94–96]. The required tidal volume can be determined first by setting the pressure control mode with a pressure gradient between a PEEP level of 5 cmH_2O and a peak inspiratory pressure of 10 cmH_2O as well as a T_i of 0.6 s. These variables will dictate the respiration rate and the primary tidal volume. Then, based on the end-tidal carbon dioxide tension, the driving pressure should be adjusted (<13 cmH_2O) to obtain the targeted values. In a second step, the resultant tidal volume will be maintained as ventilation is switched to PRVC without changing other settings.

Titrating the inspired oxygen fraction (FiO_2) in preterm and term neonates is not straightforward. It is important to avoid excessive inspired concentrations as the resulting oxidative stress contributes to potential major organ injuries including effects in the lung, brain, and eyes [97]. In addition, given the large affinity of fetal hemoglobin for O_2 and the shape of the oxyhemoglobin dissociation curve, an arterial oxygen saturation (SaO_2) >92% may not accurately correlate with the arterial partial pressure of oxygen (PaO_2). Hence, small fluctuations in the SaO_2 may reflect very large fluctuations in the PaO_2 [98]. Knowing the particular harm that an excess of oxygen may cause in preterm and full-term neonates, the inspired oxygen fraction should be titrated to target a SaO_2 between ~90 and ~94% [99, 100]. Setting a minimum FiO_2 after induction of anesthesia would also benefit identifying the loss in lung volume and decrease in FRC, which are at the root of intraoperative hypoxemia in infants. Thus, when SaO_2 decreases in a neonate or infant, ventilation/perfusion mismatch should be suspected. A recruitment maneuver at any FiO_2 will re-establish an acceptable SaO_2, which may be maintained with an adequate level of PEEP. Hence, it is prudent to maintain the FiO_2 at ~30–35% during anesthesia in neonates to identify intraoperative alveolar closure as soon as it occurs and initiate a recruitment maneuver.

Key Points

- Hypoxia and/or hypocapnia are the major burden during mechanical ventilation.
- Pressure regulated volume control is the most appropriate mode in neonate as the inspiratory decelerating flow will adapt continuously to the changing respiratory compliance.
- The inspired oxygen fraction should be titrated to avoid hyperoxia and to detect early onset of ventilation/perfusion mismatch.

Monitoring of Ventilation

Although real-time pulmonary monitoring is essential to interpret the changes in lung physiology that occur during mechanical ventilation in neonates, it is crucial to associate the information obtained from different waveforms displayed by the ventilators and the output on gas exchange and tissue oxygenation. Applying a protective open-lung ventilation strategy requires adaptation of the ventilator settings according to this real-time pulmonary monitoring. Most ventilators available in the operating theatre display continuous waveforms of pressure, volume, flow, and loops, as well as automatically derived respiratory mechanical variables. The classical pulmonary waveforms are represented by pressure, volume, and flow displayed versus time. The pressure and flow curves are specific for the ventilation mode used and thus, while displaying the pressure curve is essential during VCV (since pressure is the dependent variable), it is equally important to focus on the flow versus time curve in the PCV mode since the effectiveness of alveolar ventilation depends on the greatest extent on the flow waveform. This allows the anesthesiologist to detect: (i) an interruption in the inspiratory waveform, indicating insufficient time to equilibrate the alveolar and airway pressures, with the risk being inadequate lung inflation, and (ii) an incomplete deflation of the lung with the risk of auto-PEEP, overdistension of the lung, and an enhanced risk of barotrauma. Thus, in terms of the flow curve, it is essential to adjust both T_i and T_e (either by changing the ratio or by decreasing the respiratory rate) to let the waveform reach the zero-flow state before transitioning to the next insufflation or exsufflation [101].

The pressure–volume and flow–volume loops afford an insight into the respiratory mechanics during mechanical ventilation, namely the respiratory system compliance and resistance. The flow–volume loop is very useful to detect changes in the inspiratory or expiratory resistances. For instance, increases in airway resistance are obvious in the flow–volume curve with a decrease in the expiratory flow peak, which is expressed by a concave expiration loop. Moreover, an incomplete flow–volume loop indicates an air leak, which can occur in neonates with uncuffed tracheal tubes are present. The dynamic pressure–volume (P–V) loop, which is displayed by the ventilator, describes the mechanical behavior of the respiratory system during inflation and deflation and includes the resistive and convective acceleration components of flow. Thus, the dynamic P–V curve provides essential information to track the dynamic trends of the respiratory system compliance (defined by the slope of the loop), as well as tidal volume. Although some information can be obtained from the curve to help determine the "best" PEEP, the beginning of the dynamic inspiration provides evidence on lung recruitment from tidal ventilation, independent of PEEP [102], particularly during PCV when the pressure remains constant. Conversely, when ventilating with a constant flow such as under VCV, the P–V loop may detect overdistension of the lung as evidenced by a change in the slope of the inspiratory P–V curve, namely the upper inflection point. The lower inflection point at the lower part of the loop corresponds to the beginning of an alveolar recruitment. This may provide insight into the importance of airway closure.

The automatically derived values displayed by the ventilator should be interpreted with some caution as the absolute values are global parameters including the whole respiratory system as well as the equipment (circuit, tracheal tube, filter, and so on) [103]. These values are often obtained using the interruption technique, which is based on the ratio of the pressure decrease due to the interruption of the inspiratory flow and that before the interruption. It is important to note that >40% of the values are related to the equipment itself and thus, clinicians should not rely on these absolute values to interpret physiological changes in the respiratory system itself.

An indirect monitor of ventilation recently introduced is near-infrared spectroscopy (NIRS), a noninvasive technique for monitoring tissue oxygenation and perfusion [104, 105]. NIRS indirectly reflects ventilation via perturbations in the cerebral perfusion. Oxygenation may be a consequence of a significant cardiorespiratory interaction due to the presence of large intrathoracic pressures, which decrease the total venous return and thus, cardiac output. The cerebrovascular reactivity to carbon dioxide, particularly in preterm and full-term neonates, is another major factor affecting cerebral perfusion and may indirectly indicate an inappropriate ventilator setting.

Key Points

- Flow versus time curve and pressure–volume loop are essential to adapt the ventilation strategy.
- The near-infrared spectroscopy should be considered as an important indirect monitoring of mechanical ventilation.
- A decrease in oxygen regional saturation may be due to a decrease in cerebral perfusion as a consequence of decrease in cardiac output or vasoconstriction due to hypocapnia.

Conclusion

There is growing evidence of the benefit of applying an open and protective lung strategy in neonates. Over the past two decades, technological advances have introduced several new ventilation modes, which have undoubtedly advanced neonatal ventilation. Although the superiority of one ventilation mode over another in terms of neonatal pulmonary and neural outcomes has not been established, there is some evidence that pressure-regulated volume control may provide the most appropriate ventilation mode. However, the remaining challenge is to determine how best to mechanically ventilate the lungs based on respiratory physiology of the preterm and full-term neonate to optimize lung volume and guarantee adequate tissue oxygenation without augmenting lung stress and strain, which may induce lung injury (particularly in the immature lung) and lead to serious hemodynamic consequences with subsequent adverse neurological and metabolic outcomes.

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Perioperative Monitoring: Methods, Implementation, and Interpretation

7

Nicola Disma and Christian Breschan

Introduction

Comprehensive, accurate, timely, and absolutely reliable monitoring is an essential objective for the safe and successful management of the neonate during surgery. The achievement of this objective is complicated by two main factors:

1. The small size of the infant increases the difficulty in applying all types of instrumentation, especially those pertaining to vascular access. In addition, the neonate is frequently completely covered during surgery and out of sight or easy reach by the anesthesiologist. Thus, visual observation of the neonate is impossible, leaving the anesthesiologist completely dependent upon the applied monitors. All monitoring lines, probes, or catheters must be functioning perfectly before surgery commences and be protected against any possible compromise intraoperatively, such as pressure from the drapes, surgeons' arms, or other equipment. Sampling respiratory gases or blood is also complicated by the small volumes that may be withdrawn from the neonate.
2. The extremely dynamic physiology of the neonate may result in very rapid changes in important parameters. Monitoring systems must be capable of responding instantly to these changes and promptly alerting the anesthesiologist of these changes.

This chapter describes and discusses methods for perioperative monitoring of the cardiorespiratory, neurological, and metabolic state of the neonate. The monitors described vary from the simple and noninvasive to the complex and invasive. The selection of the extent of monitoring required for any individual neonate will depend upon the severity of the medical/surgical condition and the proposed surgery. It is assumed that neonatal surgery will only be performed in hospital units that have the appropriate equipment to properly monitor the neonate.

Cardiorespiratory Monitoring

Precordial Stethoscope

The precordial stethoscope is the original and simplest method to monitor cardiorespiratory homeostasis in neonates and infants. It is positioned on the child's left precordium to auscultate both the heart and lungs. However, this monitor has been widely supplanted by newer technologies [1]. Nevertheless, the stethoscope deserves mention as it can be applied at zero cost in any case where other techniques are either unavailable or unaffordable. If used continuously, this monitor may immediately warn of a significant change, which can be confirmed by other monitors. Recently, pre-tracheal application of a stethoscope has also been described to detect adverse events in special areas such as the MRI suite. This monitor was the first to diagnose adverse events compared with capnography and oximetry (by almost four-fold) [2].

The esophageal stethoscope was originally described to monitor small patients during thoracic surgery [3]. It is also used less frequently today than in the past, but may be valuable in some cases [4]. The stethoscope probe may be combined with an esophageal temperature probe and esophageal ECG leads (E-Probe, Cardell® Esophageal Probe).

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Arterial Hemoglobin Oxygen Saturation—Pulse Oximetry

Pulse oximetry was introduced into clinical practice in the 1980s and rapidly became an indispensable aid to management of the neonate in the perioperative period. The pulse oximeter probe consists of two light-emitting diodes (LEDs) that emit red and infrared light, with a semiconductor as a detector. Pulse oximetry relies on the Beer-Lambert law, which relates the concentration of a chromophore to light absorption, optical path length, and extinction coefficient. In pulse oximetry, the chromophores to be detected are oxyhemoglobin and deoxyhemoglobin. Two wavelengths (660 and 940 nm) in which the extinction coefficient of oxy- and deoxyhemoglobin differ are required to determine the oxygen saturation. Fetal hemoglobin (HbF) and adult hemoglobin (HbA) have similar absorption spectrum and thus pulse oximetry is equally accurate in neonates as in adults. The pulse oximeter calculates oxygen saturation as the ratio (R) of absorbance of the pulsatile versus the nonpulsatile optical signal at two wavelengths, represented by:

$$R = \left(AC_{660} / DC_{660}\right) / AC_{940} / DC_{940})$$

where AC is the pulsatile signal and DC is the nonpulsatile signal at 660 and 940 nm, respectively. The pulse oximeter converts R to oxygen saturation through an empirically derived curve (Fig. 7.1). The relationship between R and arterial saturation is curvilinear, but closely approximates a straight line over a 20% range in arterial saturation. The calibration curve was constructed using healthy adults who breathed hypoxic gas mixtures and compared the R value to the CO-oximeter-measured arterial saturation [5]. This calibration curve was based on arterial saturation values ranging from 80 to 100%; values less than 80% are extrapolated from the curve and are less accurate because of the curvilinearity of the calibration curve (Fig. 7.1). However, it is possible to construct a calibration curve over a range other than 80–100%. For example, the Masimo "Blue Sensor" is calibrated for arterial saturations between 60 and 80%, and designed for use in infants 2.5–30 kg with conditions associated with low arterial saturations [6]. The Blue Sensor does measure arterial saturations of <60% although the accuracy is similar to two other oximeters [6].

Pulse Oximetry Use in Clinical Practice

Optimally, the LED and the detector should be placed exactly opposite to each other with 5–10 mm of intervening tissue. Low saturation readings or a failure to detect a saturation may occur if components of the probe are not exactly aligned [7]. In neonates, the probe is commonly placed across the thumb (if large enough), the palm of the hand, the lateral aspect of the foot or the wrist, but it may also be applied to the ear lobe, cheek, or tongue (Fig. 7.2) [8]. These positions are highly successful in neonates because their bones are not calcified, thus facilitating reliable measurements [9]. Pulse oximeters vary in their performance, but most claim an accuracy of ±2–4% or less at saturations >80%. As mentioned, pulse oximeters are less accurate at low saturations. Hence, during profound desaturations, their accuracy cannot be relied upon. It is also important to realize that the top of the oxyhemoglobin desaturation curve is flat; hence, at high saturations, relatively large changes in arterial pO_2 occur with

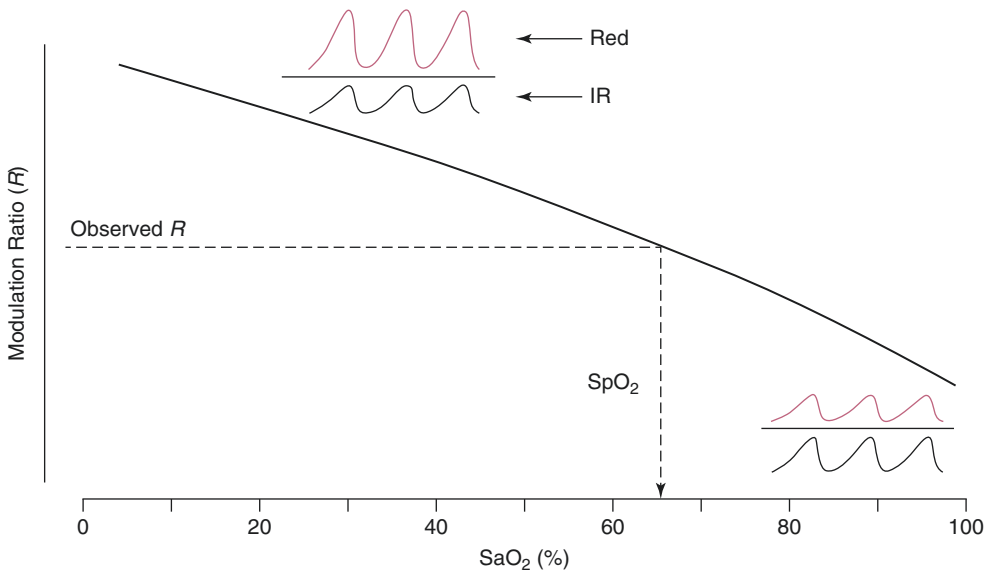

Fig. 7.1 Calibration curve of pulse oximetry. The oximeter converts the ratio, R, to an oxygen saturation through an empirically derived curve

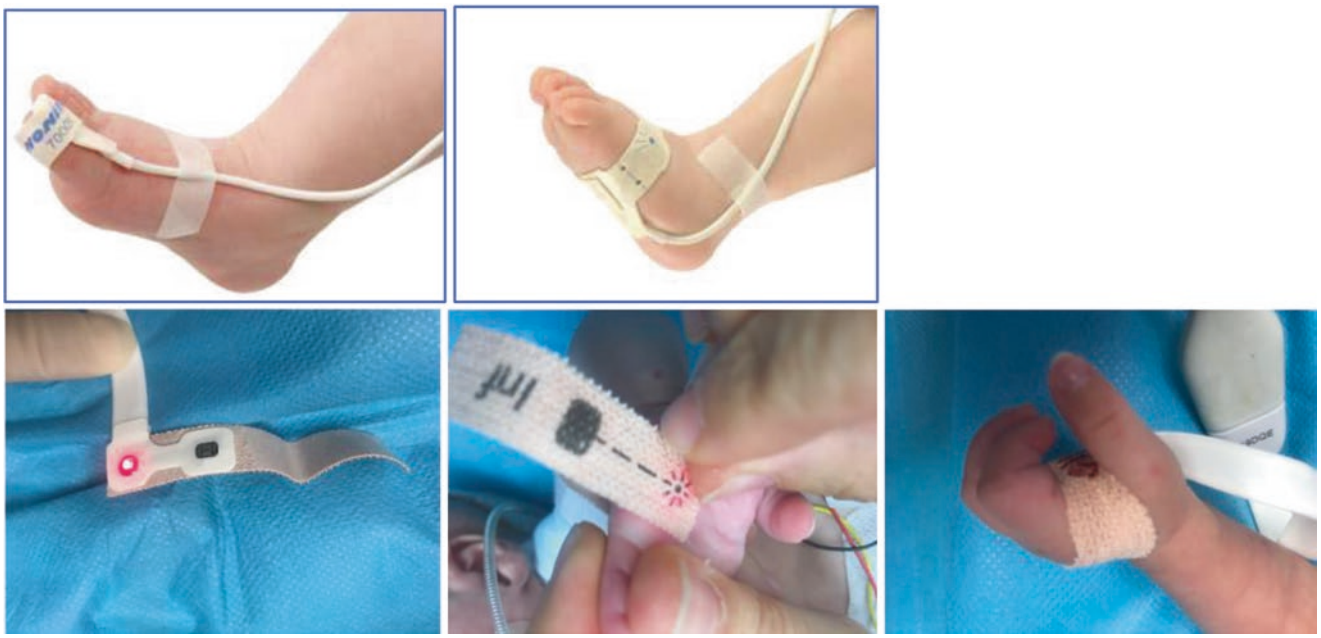

Fig. 7.2 Correct positioning of the pulse oximeter probe on the finger, foot and hand of the neonate

only minor changes in saturation. Thus, there has been continuing difficulty in defining a "safe" target saturation for the preterm infant in order to avoid the consequences of hyperoxia [10–12]. Ideally, intraoperative oxygen saturation should be maintained at approximately 90–93% to avoid hyperoxia and ophthalmic and pulmonary adverse events (see Chaps. 2 and 17).

Different models of pulse oximeter vary in their response time to physiological changes in the patient [13]. In general, the most recent models with "signal extraction technology" have faster response times and more precise measurement. They are also less affected by motion.

The pulse oximeter is extremely useful in neonates because intraoperative desaturation occurs most frequently in this age group [14]. However, the oximeter is subject to interference from several factors. Motion artifact is usually not a problem during anesthesia but may be significant during the induction and recovery phases. To prevent this problem, use models with signal extraction technology (e.g., Masimo), which suppresses the effect of motion on the oximeter signal [13]. A strong external light source may also affect the oximeter's performance. The probe should be covered (aluminum foil is ideal) to exclude extraneous light and protected by a rigid frame to prevent pressure on the sensor. In low perfusion states (see below), the signals may not be adequate for interpretation and no result will be displayed. Under these conditions, later model machines may perform better or apply an ear probe to the pinna to ensure a continuous oximeter display [15].

The performance of the pulse oximeter is unaffected by changes in the hematocrit, hemoglobin, and bilirubin concentrations. However, pulse oximetry has limitations when physiological changes occur. Under conditions of hypothermia, vasoconstriction, and hypotension, pulse oximeters are less accurate and less reliable. During moderate hypoxemia, the oximeter measurements may exceed the actual oxygen saturation, although during acute desaturations, oximeters usually underestimate the actual saturation. If methemoglobinemia is present, the SpO_2 becomes 85% regardless of the actual arterial saturation because of the absorbance spectra of methemoglobin relative to hemoglobin. After carbon monoxide exposure, SpO_2 overestimates arterial saturation because carboxy and oxyhemoglobin absorb red light similarly. In bronze baby syndrome, which may occur after phototherapy, SpO_2 readings become unreliable [16]. Dark skin pigmentation may also cause falsely low readings especially at lower levels of saturation (<80%) [8].

In summary, the most common reasons for inaccurate SpO_2 measurement are:

- Misalignment of the probe sensors due to the site chosen;
- Low oxygen saturation (<80%) when using a standard oximeter;
- Inadequate tissue perfusion (hypotension, hypothermia, etc.);
- Bronze skin (due to phototherapy) or dark pigmentation;
- Equipment malfunction/disturbance including motion artifact, incorrect probe size, or strong external light.

Complications have been reported from the application of oximeter sensors [17, 18]. When applying sensors circumfer-

entially to the finger, caution must be exercised to avoid applying the sensor too tightly, which might cause ischemic injury [17, 18]. When a reusable clip-type sensor is used on the ear, care should be taken to ensure that the clip does not exert excessive pressure and cause ischemia to the underlying tissue [14]. Burns and pressure necrosis at the site of the probe have also been reported in neonates [18].

Clinical Application of Pulse Oximetry

In neonatal anesthesia practice, it is often advantageous to apply two separate pulse oximeter probes. In some cases, it may be useful to monitor both pre-ductal (right arm or head) and postductal saturation (a foot) and in others, the second probe may act simply as a backup should the first probe fail [19]. Pre- and postductal pulse oximetry may serve as a useful guide in certain conditions. A decrease in the postductal SpO_2 of more than 10% compared with pre-ductal SpO_2 indicates significant pulmonary hypertension, right-to-left shunt at the patent ductus arteriosus (PDA) and shift toward fetal circulation. If a right-to-left shunt occurs at the level of the foramen ovale, no difference in oxygen saturation will be apparent between the two oximeters. In clinical conditions such as single ventricle physiology, pulmonary atresia, or transposition of great arteries, maintenance of the transitional circulation is essential to maintain pulmonary and/or systemic blood flow. Monitoring SpO_2 estimates the ratio between the pulmonary flow and systemic flow (Qp/Qs) and can serve to gauge the balance of pulmonary to systemic blood flow.

Monitoring SpO_2 can also track changes in the arterial oxygenation from the fetus to the neonate during the first minutes after birth. During fetal life, the normal SpO_2 is approximately 72% whereas during the initial hours after birth, there is a rapid and steady increase in SpO_2 to the mid-90s [20]. Pulse oximetry has also been evaluated as a screening tool for congenital heart disease in the newborn nursery. If SpO_2 does not increase to values in the mid-90s by day 2 of life, the presence of cyanotic congenital heart disease should be contemplated. The specificity and sensitivity of pulse oximetry to diagnose cyanotic congenital heart disease, 99% and 72% respectively, are superior to a clinical evaluation [21, 22].

An excessive concentration of oxygen in preterm infants contributes to the development of retinopathy of prematurity. In extremely preterm infants (24–27 weeks), the risk of developing retinopathy of prematurity depends on the duration and timing of the supplemental oxygen [23]. To limit the risk of this complication, the SpO_2 should be maintained in the range of 90–93% (see Chaps. 2 and 17). Although an SpO_2 <90% reduces the risk of retinopathy of prematurity even further, it increases the mortality rate and is thus not recommended [12, 24]. This has been confirmed recently in a meta-analysis of five randomized clinical trials that included 4965 infants [25]. Excessive oxygen administration may also be deleterious during resuscitation [12, 26]. During neonatal resuscitation, the American Heart Association recommends monitoring the pre-ductal SpO_2 to titrate the oxygen administration [27].

Electrocardiography (ECG)

ECG is based on the principle of detecting electric potentials that originate in the heart across vectors through the chest. It represents an essential part of routine intraoperative monitoring at any patient's age, with the aim of immediately detecting cardiac arrhythmias or myocardial ischemia. The three lead ECG, routinely used during anesthesia, mainly detects alterations in cardiac rate or rhythm, the commonest changes in the pediatric age group (Fig. 7.3). However, in special circumstances where an ischemic lesion of the myocardium is possible, ventricular leads should be applied.

The most frequent ECG alterations in neonates and infants undergoing anesthesia are tachyarrhythmias (sinus, atrial, and supraventricular tachycardia (SVT)) and bradyarrhythmias (sinus bradycardia and junctional bradycardia). Tachycardia is mainly due to inadequate depth of anesthesia during airway manipulation or surgical stimulus or hypovolemia. Bradycardia is usually caused by hypoxia or vagal stimuli.

The challenge during ECG monitoring in neonates is their physiological propensity to tachycardia. Heart rates between 100 and 150 beats per minute (bpm) are considered normal in term neonates. Consequently, discriminating between sinus tachycardia and SVT can be difficult as the P-wave is not always apparent on the ECG monitor. For this reason, ECG changes must be evaluated together with the whole clinical picture of the neonate, while also considering the possibility of artifacts.

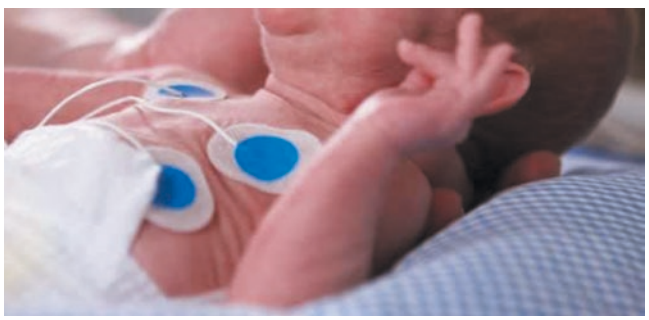

Fig. 7.3 Electrocardiographic electrode positioning in neonates

Advanced Pulse CO-Oximetry and Oxygen Reserve Index (ORI)

Advanced pulse oximeter technologies can detect hypovolemia, hypoperfusion, and anemia noninvasively, all of which occur commonly during neonatal surgery. These conditions are difficult to monitor in neonates because insertion of arterial catheters and blood sampling remain challenging in this population. Thus, a reliable and noninvasive measurement is a great help for clinicians.

Advances in optical technologies, especially light emitting diodes (LEDs), permitted the development of pulse CO-oximetry. Conventional pulse oximetry founded in the 1980s used two LEDs at 660 nm and 940 nm, respectively, which were the only commercially available LEDs at that time. Fortunately, the absorption spectrum of oxy- and deoxyhemoglobin were well differentiated at those wavelengths, which permitted the measurement of SpO_2. However, carboxyhemoglobin and methemoglobin were not differentiated, and thus conventional pulse oximetry was unable to determine them or the total hemoglobin concentration. In the near red and infrared region, many LEDs are now commercially available, which permit multiwavelength pulse oximetry to measure all hemoglobin species as well as total hemoglobin concentration (SpHb). In addition, intravascular volume and perfusion status can be monitored through the plethysmograph variability index (PVI) and perfusion index (PI), which analyze the optical signals in a specific manner.

PI and PVI are determined by evaluating the interrelation between the cardiovascular and respiratory system to detect hemodynamic changes indicative of circulating blood volume and peripheral perfusion. This is similar to assessing the effect of ventilation on the pulse pressure during invasive monitoring of the arterial waveform (Fig. 7.4a). This pulse pressure variation depends on the mode of ventilation. The effects on venous return, right ventricle afterload, left ventricle end diastolic pressure, and left ventricle afterload differ during spontaneous or positive pressure ventilation. This dynamic ventilator-linked variation in arterial pulse pressure and systolic blood pressure may be interpreted as a sensitive indicator of circulating blood volume. It is as accurate as measuring the central venous pressure and pulmonary artery occlusion pressure.

PI and PVI are the optical signal components that correlate with the systolic wave amplitude and the systolic wave variation with ventilation, respectively, on the arterial waveform (Fig. 7.4b). The PI is the amplitude difference between the pulsatile and nonpulsatile optical signals and is displayed as a percent of the nonpulsatile optical signal, which remains constant and represented by:

$$PI = AC / DC \times 100\%$$

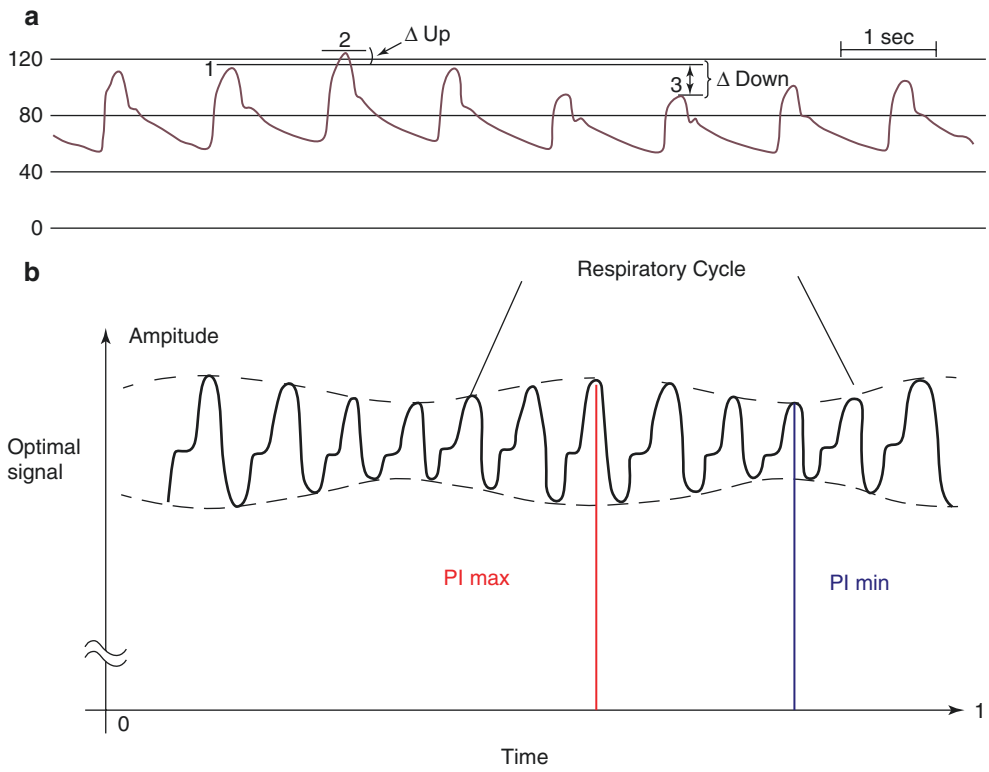

Fig. 7.4 (**a**) Respiratory variation in the pulse pressure with ventilation during invasive monitoring of the arterial waveform. These hemodynamic changes are indicative of circulating blood volume and peripheral perfusion. (**b**) Plethysmograph variability index (PVI) and perfusion index (PI) are the optical signal components that correlate with the systolic amplitude and the systolic amplitude variation with ventilation, respectively, on the arterial waveform

where AC is the amplitude of the alternating pulsatile signal and DC is the amplitude of the direct, nonpulsatile signal. PI directly correlates with the strength of the pulsatile optical signal, which correlates with the strength of the manual pulse (Fig. 7.4b). The PI ranges from 0.02 to 20%, although values greater than 1% generally represent normal physiologic conditions. PVI is measured from changes in the PI during a ventilator cycle. PVI is calculated as the difference between the maximum and minimum PI divided by the maximum PI during a cycle, as shown by:

$$\mathrm{PVI} = \left(\mathrm{PI}_{\max} - \mathrm{PI}_{\min}\right) / \mathrm{PI}_{\max}$$

PVI is reported as a percentage (0–100%), in which larger values correspond to greater pulse oximeter amplitude waveform differences during the respiratory cycle, which correlate with the severity of hypovolemia. If hypotension is present, PVI greater than 12–14% indicates hypovolemia for which an intravenous fluid bolus will improve the arterial pressure.

Studies in neonates suggest that PI may have clinical utility. Immediately after birth, PI predicts the development of chorioamnionitis, a condition associated with significant morbidity and mortality. PI had a 93.7% positive predictive value and 100% negative predictive value in identifying subclinical chorioamnionitis; early detection enabled early treatment, which decreased the disease severity and admission to a neonatal critical care unit [28]. Similarly, PI has been evaluated to predict the severity of illness for other conditions in neonates [29]. PI correlated closely with the Score for Neonatal Acute Physiology, with a 91.2% positive predictive value and 96.8% negative predictive value. However, PVI has been proven to be highly variable on the same and different limbs in the same stable, preterm infant [30]. On the other hand, PVI may be a useful noninvasive metric in assessing the volume responsiveness of ventilated neonates during surgery [31, 32].

Pulse CO-oximetry detects changes in the hemoglobin concentration during surgery earlier than conventional blood draw-based laboratory measurements. This decreases the number of blood samples needed and guides blood transfusion decisions [33]. Like conventional pulse oximetry, erroneous measurements occur during severe hyperbilirubinemia and in the presence of intravascular dyes such as methylene blue. In 52 preterm neonates weighing <3 kg, the bias and precision of SpHb compared with laboratory blood measurements were 0.09 ± 1.67 g/dL, with an r-squared value of 0.48 [34]. Advances in the development of sensor size will soon cement the use of this technology in neonates.

Oxygen Reserve Index (ORI)

It is often difficult to evaluate the clinical importance of a brief, single decrease in SpO_2 in pediatric patients. Coté et al. defined "major" events as those in which SpO_2 was <85% for >30 s and "minor" events as SpO_2 <85% for <30 s, although there was no neurocognitive outcome data to validate the clinical relevance of these definitions [35]. Alternatively, others consider an SpO_2 <90% to be significant [36]. Thus, improving oxygenation (through improving ventilation, alveolar recruitment, and an increased FiO_2) is recommended for an SpO_2 ≤90%.

The oxygen–hemoglobin dissociation curve is a graphical display of the proportion of saturated hemoglobin on the ordinate against the oxygen partial pressure in blood (PaO_2) on the abscissa (Fig. 7.5a). The dissociation curve is experimentally determined from in vitro titration of blood with increasing PaO_2. For very low PaO_2 values, the SpO_2 increases minimally for a given change in PaO_2. However, for PaO_2 values between 20 and 60 mmHg, the SpO_2 increases linearly and steadily. Beyond a PaO_2 of 60 mmHg, the SpO_2 once again levels off and increases minimally between 90 and 100%.

The difficulty with the pulse oximeter is that there is a broad range of PaO_2 (i.e., from 100 to >700 mmHg) over which the SpO_2 remains almost constant, at 100% (Fig. 7.5b). Using the saturation alone, clinicians are unable to determine the PaO_2 without blood-gas analysis, the latter being impractical or too slow in many situations. When there is a rapid decrease of oxygen reserves (as occurs during an apneic spell), clinicians are unable to quantify a decrease in the PaO_2 until the SpO_2 begins to decrease, which occurs at PaO_2 values <100 mmHg.

Clinically, it would be useful to have a real-time, continuous, noninvasive estimation of the PaO_2, especially in patients who are receiving supplemental oxygen and whose PaO_2 is >100 mmHg.

Recently, Masimo developed the oxygen reserve index (ORI) monitor, which uses their FDA-approved noninvasive hemoglobin sensor to estimate oxygenation in the low hyperoxic range, from a PaO_2 of ~100 to ~200 mmHg [37]. The ORI, a dimensionless index that ranges from 1 to 0, is calculated from a proprietary algorithm based on infrared absorption values obtained from the Masimo pulse CO-oximeter. The sensor uses absorption of seven wavelengths of light to estimate blood constituents. The ORI algorithm combines the Fick principle with the infrared absorption properties of both arterial and venous hemoglobin. By replacing some variables in a chain of equations, the oxygen saturation of venous blood (SvO_2) is directly proportional to PaO_2 at constant oxygen consumption and cardiac output. As PaO_2 increases beyond 100 mmHg, SvO_2 continues to increase until it reaches full saturation at a PaO_2 of ~200 mmHg. Monitoring the ORI may signal impending desaturation and a means to avoid hyperoxia in neonates, but this remains to be confirmed.

When utilized in conjunction with SpO_2 monitoring, ORI is intended to provide real-time visibility from hypoxia to the

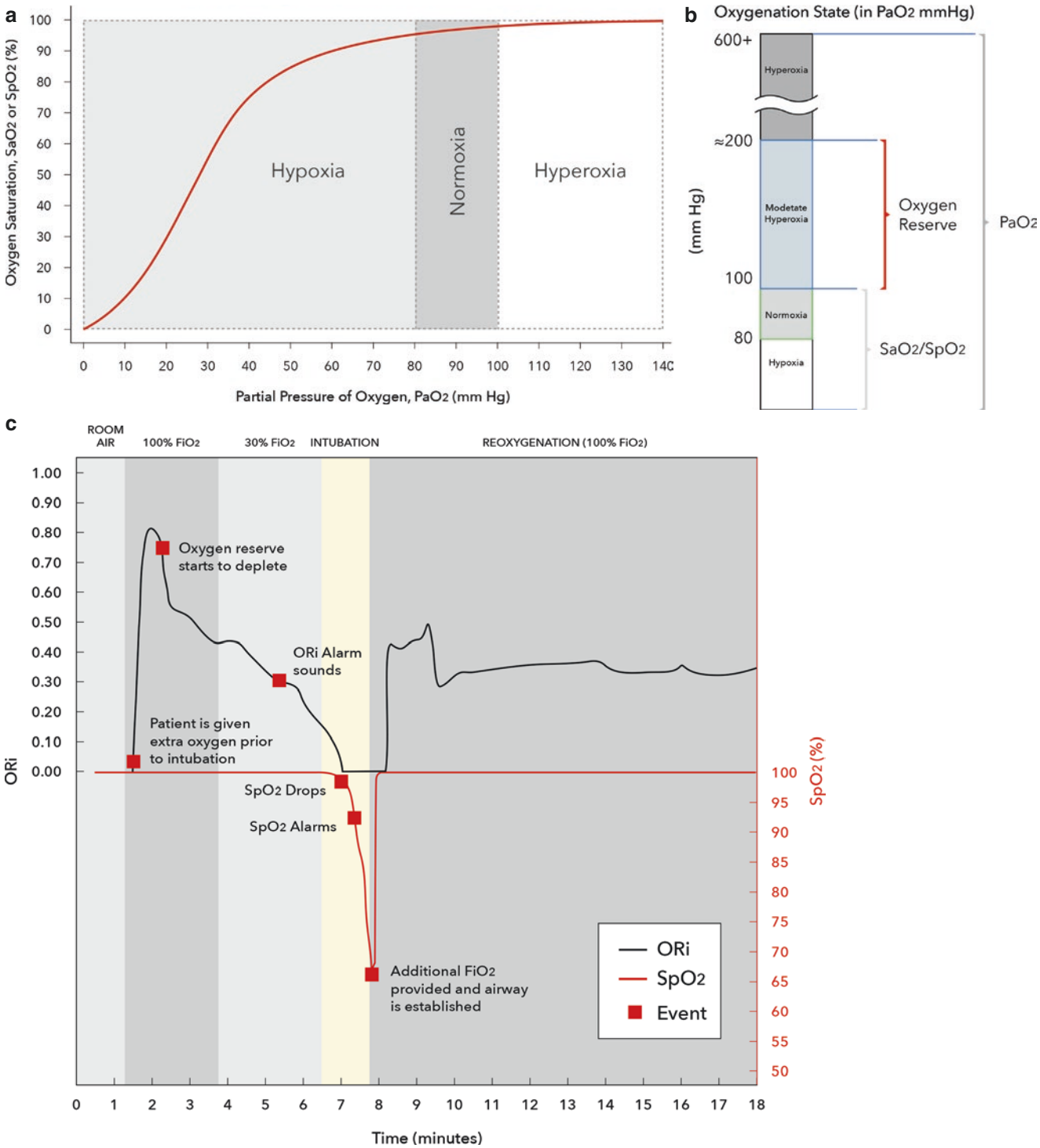

Fig. 7.5 (**a**) The oxygen–hemoglobin dissociation curve. Reproduced from https://www.masimo.it/siteassets/it/documents/pdf/plm-10728a_brochure_ori_italian.pdf. (**b**) Oxygenation state. PaO_2 between 100 and 200 mmHg is defined as "moderate hyperoxia". Reproduced from https://www.masimo.it/siteassets/it/documents/pdf/plm-10728a_brochure_ori_italian.pdf. (**c**) Use of ORI for real-time visibility from hypoxia to the moderate hyperoxic state. Reproduced from https://www.masimo.it/siteassets/it/documents/pdf/plm-10728a_brochure_ori_italian.pdf

moderate hyperoxic state (Fig. 7.5c). When the ORI is <0.30, it may provide advance warning of a decreasing PaO_2 despite an SpO_2 reading >98% and that the PaO_2 remains in excess of the PaO_2 at which the SaO_2 decreases rapidly. In a recent pilot study of 25 healthy children under general anesthesia, the ORI detected impending desaturation 31.5 s before changes in SpO_2 were detected. Even 30 s of advanced warning of impending desaturation might give clinicians enough time to implement corrective actions and avoid an insult [38]. ORI is not intended to replace SpO_2 or PaO_2 monitoring, but to integrate these metrics to provide advance warning to allow time for corrective action. Of all age groups, neonates are at the greatest risk for acute oxyhemoglobin desaturation. Preventing this in neonates could dramatically improve perioperative morbidity in this age group. Further studies are required to confirm the effectiveness of this monitor.

Inspired and Expired Gas Analysis

The measurement of oxygen, carbon dioxide, and inhaled anesthetic agents in the airway remains an important aspect of safe anesthesia practice. Originally, these concentrations were measured by mass spectrometry. However, as technology developed, this was replaced by infrared spectrophotometry; the absorption spectra for CO_2, N_2O, and inhaled anesthetics differ, ranging from 7 to 13 μm. As with pulse oximetry and near-infrared spectroscopy (NIRS), the concentration of the gases is calculated using the Beer-Lambert law. Oxygen concentration cannot be measured by this technique because it does not absorb infrared light; rather, it is measured by electrochemical or paramagnetic methods.

Expired CO_2 concentration or end-tidal CO_2 ($EtCO_2$) can be plotted against time to illustrate changes in the concentration of CO_2 during inspiration and expiration. The continuous measurement of $EtCO_2$ is a standard of care in anesthesia practice.

One of the following two sampling methods is used to monitor $EtCO_2$: sidestream or mainstream capnography [39].

Sidestream Capnography

Sidestream capnography utilizes small caliber tubing connected to the breathing circuit to continuously aspirate gas from the breathing circuit and direct it to a spectrophotometry cell in the capnometer. The flow sampling rates are optimal between 50 and 200 mL/min, although some monitors use rates as large as 400 mL/min. Gas samples for sidestream monitoring may be collected either at the level of the tracheal tube connector or at the tip of the tracheal tube. If collected at the connector, the use of a very low dead space system with a "baffle" between the Y-connector of the circuit and the sampling port is desirable, as well as a small fresh gas flow to minimize dilution of the aspirated sample and thus the end-tidal gas concentrations with fresh gas [40]. Sidestream sampling using low sampling rates (50 mL/min) from a low dead space (0.5 mL) tracheal tube adaptor in low birth weight infants significantly underestimated $PaCO_2$ levels, but did detect excessively high and low levels [41]. Samples collected from the tip of the tracheal tube correlated much better with $PaCO_2$ levels [42], even in the presence of severe lung disease [41, 44]. Infant-size tracheal tubes with a fine second sampling channel external to the lumen of the tube are available for this purpose (Mallinckrodt™ Oral/Nasal Tracheal Tube Cuffless Monitoring Lumen, Sizes 2.5 and larger). Unfortunately, the fine aspirating channel is prone to blockage by secretions [41].

In neonates, high-flow gas sampling should not be used because it will entrain fresh gas or inspiratory gas in the sample, thereby diluting the $EtCO_2$. This may also dramatically decrease alveolar ventilation if the set tidal volume is small. Other potential problems include water vapor condensation obstructing the tubing, leaks or disconnections at the CO_2 analyzer, and a delay of several seconds between actual and monitored changes in the $EtCO_2$. A practical consideration at the present time is that most anesthesia machines are equipped with a built-in sidestream monitor.

Mainstream Capnography

Mainstream capnography incorporates the infrared analyzer within the breathing circuit, thereby eliminating the need for sampling tubing. This results in a more timely gas analysis. Mainstream capnography offers an advantage in neonates because it eliminates the risks of excessive gas sampling and errors from sampling dead space. However, its disadvantages include the weight of the analyzer, which can kink the tracheal tube, the need for frequent calibration, additional dead space, and water vapor condensation, all of which lead to errors and unreliable measurements.

The capnograph provides important clinical information during neonatal anesthesia (Fig. 7.6). The waveform is divided into an inspiratory phase and three expiratory phases. The first expiratory phase, A and B in Fig. 7.6, reflects gas in the large airways (anatomical dead space) where the $EtCO_2$ is zero (unless there is rebreathing). The second expiratory phase, B and C, is the rapid upstroke of $EtCO_2$ that results from the mixed sampling of exhaled gases from the large airways and alveoli (transitional phase). The third expiratory phase, C and D, also known as the plateau phase, reflects the $EtCO_2$ in the alveolar gas. The measured $EtCO_2$ is the value at the apex of the plateau phase before the sudden decrease in $EtCO_2$ that begins the inspiratory phase. During inspiration, the $EtCO_2$ level rapidly decreases to zero. A gradient is commonly found between the $PaCO_2$ and $EtCO_2$ (1–5 mmHg in magnitude), attributed to the physiologic alveolar dead space. This gradient may significantly increase with an increase dead space (Vd/Vt ratio) or a decrease in cardiac output. In neonates, this may be due to a right-to-left shunt associated with congenital heart disease, meconium aspira-

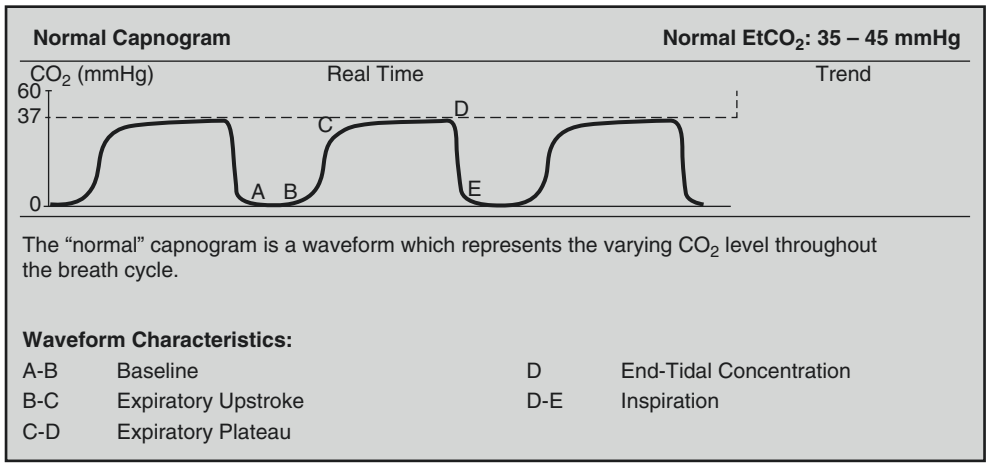

Fig. 7.6 Normal capnographic waveform

tion, respiratory distress syndrome, or shock. The correlation between $PaCO_2$ and $EtCO_2$ improves after treating preterm infants with surfactant as the Vd/Vt ratio decreases [43, 45]. Phase III of the expiratory tracing changes from a flat plateau to an upward slope when alveolar dead space increases such as with asthma. The $PaCO_2$–$EtCO_2$ gradient should be measured to gauge pulmonary function. During bronchospasm, the $EtCO_2$ tracing adopts a "Shark Fin" shape due to the slower egress of gas from obstructed airways [46].

Transcutaneous Carbon Dioxide Monitoring ($tcpCO_2$)

Equipment to measure $tcpCO_2$ is routinely used in the neonatal intensive care unit (NICU) and may also be used intraoperatively [38, 47–49]. Transcutaneous measurements more closely equate to venous levels than do end-tidal, which tend to underestimate true values [49]. Hence, $tcpCO_2$ monitoring may be preferred for situations when tight control of carbon dioxide levels is essential (e.g., hypoplastic left heart syndrome). Placement of the sensor on the forehead is associated with optimal performance and is convenient to use intraoperatively in many patients. Chronic placement has been associated rarely with burns to the skin in the past as these sensors heat the skin, although more recently, skin probes maintained at lower temperatures (38 °C instead of 42 °C) yielded equally accurate carbon dioxide measurements [50].

Apnea Monitors

Apnea monitors are in common use in the NICU and are useful during postoperative recovery, especially in the preterm infant. These monitors are classified based on detection of chest movement (transthoracic impedance), ventilation (capnography), or airflow (acoustic) [51]. Of the monitors, transthoracic impedance is the most popular. Transthoracic impedance measurement is commonly combined with ECG monitoring. A small current is transmitted from one ECG pad to another one, and changes in the impedance to this current due to the chest expansion or contraction yields the respiratory rate. Since transthoracic impedance detects chest movement but not airflow, it cannot detect obstructive apnea, which simply demonstrates an erroneous respiratory rate. Capnography as an apnea monitor in patients without instrumented airways suffers from an element of unreliability as nasal secretions may obstruct gas sampling to give spurious alarms of apnea or the neonate breathes through the mouth decreasing or eliminating the signal sensed in the nares. The proboscis modification of the nasal prongs circumvents this deficiency to a large extent by sampling exhaled gases from both the nares and the mouth. Another technology that senses the temperature of exhaled breath (Linshom®) accurately measures the respiratory rate, detects apneas, and tracks tidal volume noninvasively [52, 53]. Monitoring the airflow with acoustic sensors located on the neck or chest offers theoretical advantages over transthoracic impedance, capnography, and pulse oximetry. Acoustic apnea monitors sense vibratory sounds produced by turbulent flow in the large airways and converts a sound signal into an electrical signal from which respiratory rate is calculated. Acoustical monitoring of respiratory rate has been reported in two studies in children: in the first study, the acoustical monitor was more accurate with less bias than capnography or impedance technologies, whereas in the second, the two devices yielded similarly accurate measurements, although the acoustic monitor was better tolerated in surgical patients [54, 55]. The clinical implications of these conflicting findings are unclear.

Respiratory Volume Monitor (RVM)

A noninvasive respiratory device (ExSpiron, USA) derives Vt, RR, and hence MV from the thoracic impedance utilizing

a pair of electrodes applied to the chest [56]. This monitor reliably records the respiratory rate and can detect hypopneic or apneic episodes. The recorded MV correlated well with spirometry measurements in children between 1 and 17 years of age [57]. Total airway obstruction may be detected even in the presence of chest movements. A limitation of this device is that it only functions well when the patient is positioned supine.

Pulmonary Mechanic Monitors

Pulmonary mechanics are defined by inspiratory and expiratory tidal volumes, peak inspiratory pressure, mean airway pressure, positive end-expiratory pressure (PEEP), and inspiratory and expiratory cycle time.

Planned inspiratory tidal gas volume is selected by setting the ventilator. Traditional anesthesia ventilators then deliver this predetermined volume, which can differ substantially from the actual tidal volume, especially in neonates, because of the compliance of the breathing circuit in relation to pulmonary and chest wall compliance, and the fresh gas flows. As a result of this unpredictability, mechanical ventilation in neonates historically used a pressure control mode, which is independent of the breathing circuit compliance and fresh gas flows [58, 59]. However, during pressure preset ventilation, the actual tidal volume varies according to the total compliance and the airway resistance. Thus, tidal volume may suffer if total compliance decreases or airway resistance increases. Examples of such situations include laparoscopic or thorascopic surgery, insertion of chest or abdominal sponges or retractors, tracheal tube obstruction, or pulmonary edema.

Advances in the anesthesia ventilators have made the delivery of predetermined tidal volumes more predictable during volume control ventilation. These anesthesia machines monitor compliance in the breathing circuit and compensate for it by adjusting the delivered tidal volume, for example, when fresh gas flows or compliance changes. A common circumstance that changes compliance in the breathing circuit is contraction or expansion of the tubing of the breathing circuit. The anesthesia workstation compliance tests, which are part of the machine check, compensate for the compliance of different breathing circuits. Thus, the compliance test must be repeated if the circuit is changed in any way after testing. When the tidal volume of contemporary anesthesia ventilators was set to volume control mode in a model lung with different compliances, volume control ventilation was effective in anesthetized neonates [60]. However, despite these compensatory mechanisms, modern ventilators are unable to compensate for large circuit gas leaks regardless of whether volume or pressure control mode is selected (see Chap. 6). The use of cuffed tracheal tubes eliminates the main source of circuit leaks in neonates.

During a normal breath, the expired tidal volume is less than the inspired tidal volume because of the greater oxygen uptake at the alveolar–capillary membrane compared with the carbon dioxide output from the capillaries into the alveoli. Measurement of the expired tidal volume occurs close to the expiratory valve, which tends to overestimate the actual volume due again to the compliance of the circuit.

Monitoring peak inspiratory pressure and tidal volume in neonates provides information about lung compliance and airway resistance to detect conditions such as an endobronchial intubation, bronchospasm, and tracheal tube obstruction. Monitoring these variables also helps to prevent volutrauma or barotrauma during the ventilator support in the operating room, especially in neonates with pulmonary disease or immature lungs, where small tidal volumes and lower inspiratory pressures decrease the risk of bronchopulmonary dysplasia, a strategy known as permissive hypercapnia. During surgical procedures in which substantial changes in the compliance can occur, the peak inspiratory pressure setting should be adjusted to avoid pressure trauma to the lung parenchyma.

The anesthesia circuit in workstations incorporates pneumatic or electronic devices to measure airway pressure. The location of the sensor varies with the anesthesia workstation, ideally it should be closer to the tracheal tube (Y-piece) to increase its reliability. However, this location increases the dead space, and also the risks of disconnections, or tracheal tube kinking. More frequently, the location is close to the expiratory or inspiratory valves. The sensor incorporates a diaphragm connected to the breathing circuit, which distends according to the airway pressure. The sensor activates a pressure relief valve once the selected peak pressure has been reached. It also detects a leak in the system if a preset threshold pressure is not reached. Monitoring ventilatory volumes using equipment capable of accurately measuring those appropriate in neonates reduces the risk of undetected, under or overventilation, and lung trauma.

Cuffed tracheal tubes are now commonly used in neonates with infrequent complications, although few neonates were included in these reports (see Chaps. 5 and 6) [61, 62]. The pressure within the cuff should be monitored if it is inflated. However, in neonates, it is often unnecessary to inflate the cuff to prevent leaks at normal airway pressures. Some cuffed tracheal tubes (e.g., Microcuff®, Halyard Health, UK) have been approved for use in term neonates >3 kg; these tubes have not been either studied or approved for use in premature neonates or in neonates <3 kg.

Systemic Blood Pressure Monitoring

Noninvasive Blood Pressure (NIBP)

The basic noninvasive equipment to measure blood pressure is the blood pressure cuff. The width of the cuff used should be 0.44–0.55 times the mid-point circumference of the limb utilized, thus the optimal width in the full-term neonate is approximately 1 inch (Fig. 7.7) [63].

The commonly used automated blood pressure measurement systems used in the operating room are based on oscillometry. Several such NIBP devices exist. Each employs the same principle but utilizes a proprietary algorithm to extract systolic, mean, and diastolic blood pressure from a signal generated by pulse-induced pressure fluctuations within in the cuff. The amplitude of these fluctuations varies with cuff inflation pressure. If the amplitude of the fluctuation in cuff pressure is plotted as a function of cuff pressure, the result is an oscillogram. Each oscillogram will have a unique shape and set of inflection points. The algorithms are designed to derive systolic, mean, and diastolic pressure from the data stream contained in the oscillogram.

The oscillometric pulse amplitude results from small pressure changes in the cuff due to the expansion and contraction of blood vessels within the limb encircled by the cuff as blood is ejected via the arterial tree. The diastolic pressure is related to a fall-off in the rate of decrease in pulse amplitude once the peak has been achieved and the systolic pressure is related to the steepest rate of rise of pulse amplitude after a minimum value has been crossed. The point of maximum oscillation during cuff deflation is interpreted as the mean arterial pressure.

Automated noninvasive blood pressure (NIPB) greatly simplified monitoring the neonate in the operating room. The accuracy of NIBP is controversial, especially in very low birth weight infants with a low blood pressure [64–68]. This is the population most susceptible to periventricular leukomalacia, reduced cerebral blood flow (CBF), and inadequate peripheral perfusion. Studies in such neonates have shown a regular overestimation of the mean pressure by 3–8 mmHg depending on the device used to measure the NIBP [69].

In the operating room, the most accurate determination of the systolic pressure can be obtained by placing a doppler flow probe on an artery distal to the cuff [63]. As stated above, measurements taken with an automated oscillometric device tend to overestimate systolic and mean blood pressures, especially when the neonate is hypotensive [70].

In healthy infants, blood pressure measurements recorded with a cuff applied to the upper and lower extremities are normally similar. Recent evidence suggests that a discrepancy in noninvasive blood pressures between upper and lower extremities occurs in the smaller infants (<1000 g) [71]. NIBP devices should not be relied upon in sick infants or those who require extensive surgery.

Invasive Blood Pressure

Direct measurement of blood pressure using an intra-arterial line is often required in critically ill neonates and those requiring major surgery. Arterial lines may be inserted at various sites, and each has advantages and potential disadvantages.

The umbilical artery is relatively easy to access in the immediate neonatal period and has been widely used in neonatal intensive care units. However serious thromboembolic

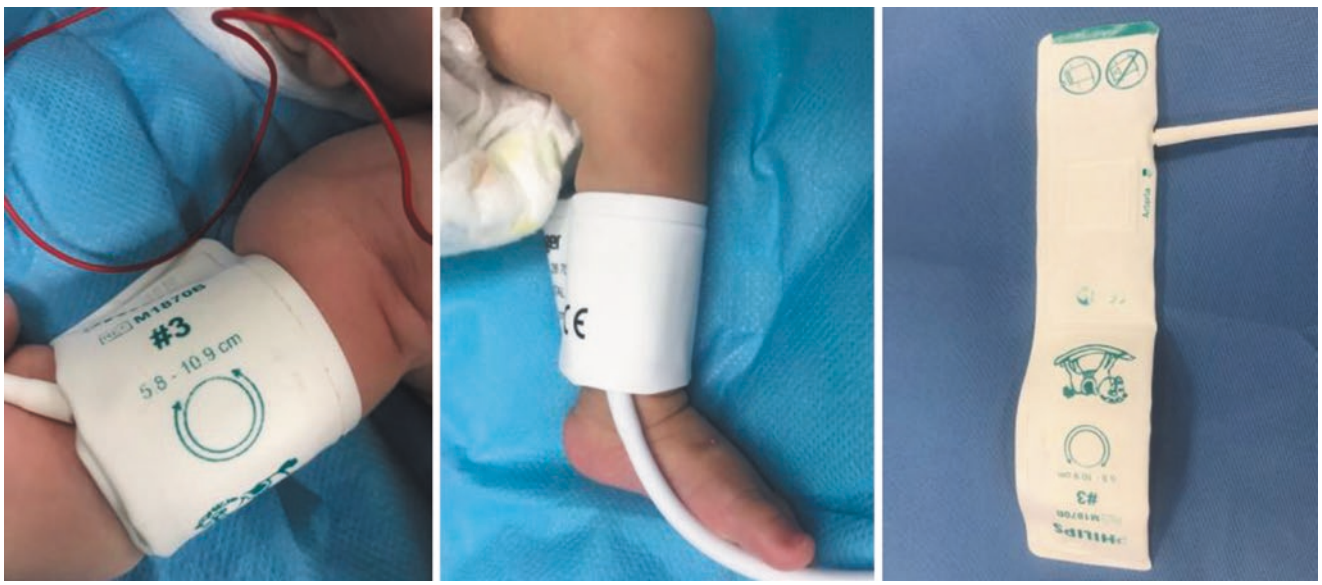

Fig. 7.7 Non-invasive blood pressure measurement, the correct cuff size and positioning

complications may follow and involve intra-abdominal organs, the lower limbs, and even the spinal cord [72]. Caution should be exercised in the choice of umbilical catheter material and design, and the fluids administered by this route. Silicon rubber catheters with an end hole are the preferred type of catheters. Hypertonic and alkaline solutions should not be administered via this route. The use of heparin in the infusion may decrease the incidence of line occlusion but does not reduce the incidence of thromboembolism [72] and poses potential problems of overdosage, especially in very small patients. When managing an infant with an umbilical artery catheter, the anesthesiologist should exercise caution at the time of withdrawing blood samples or flushing the line, especially in VLBW neonates [73]. Sampling and reinfusing rates should not exceed 1 mL in 30 s in the preterm infant. Rates in excess of this may significantly and adversely affect CBF and oxygenation [74].

Radial artery lines are more commonly used for intraoperative monitoring. Various methods have been recommended to improve the success of percutaneous insertion of a catheter in neonates. Smooth insertion of the catheter into small arteries is more likely to be attained if the level of the needle is rotated inferiorly after a flashback of blood is observed. The use of a fine guide-wire may be useful to thread the catheter into the artery, and has been demonstrated to improve success rate. If the artery cannot be palpated readily, a Doppler flowmeter probe or trans-illumination of the infant's wrist may facilitate its location (Fig. 7.8) [75]. In difficult cases, it may be necessary to use a cut-down for cannulation of the vessel. The subsequent recovery of normal arterial flow after a cut-down is no worse than after percutaneous cannulation. Allen's test of the adequacy of collateral flow to the hand is difficult to perform in smaller infants and is unreliable even in adults; hence, it is not routinely performed. Once a radial artery access has been successfully established, the limb should be immobilized on a splint and a secure continuous flush system attached. All connections should be locked. Normal saline is preferred to glucose-containing solutions for all monitoring lines [76]. Flushing of radial arterial lines should be limited to small volumes and slow rates of injection as retrograde flow into the cerebral circulation may occur with as little as 0.5 mL flush solution [77]. Blood, which has been withdrawn while taking a laboratory sample, should be reinjected into a venous access site. Similarly, aspirating blood from radial artery catheters in VLBW infants should be curtailed as it may compromise cerebral oxygenation irrespective of the speed of aspiration [78].

Fig. 7.8 Transillumitation for arterial line cannulation, using Veinlite™

Serious complications with radial artery lines are relatively rare in neonates, although instances of ischemic damage to the hand and thrombosis have been described [77, 79–81]. Any evidence of impaired circulation or skin changes distal to the catheter is an indication for its immediate removal. There is no evidence that a cut-down approach to cannulation is accompanied by increased risk of complications [82]. Rare instances of long bone growth arrest have been reported in children after both radial and femoral artery cannulation [83].

Femoral artery cannulation may be used as an alternative if radial puncture is impossible or unsuccessful, and this may better reflect true arterial pressure than the radial artery in some instances [84]. The risk of infection at the puncture site is not increased with a femoral artery cannulation. In smaller infants, the distal circulation should be carefully monitored as perfusion-related complications may occur [85]. Great care should be taken during insertion of femoral lines to avoid needle injury to the hip joint, which may cause septic arthritis and damage to the head of the femur [86]. It is extremely important that the artery be accessed caudal to the level of the inguinal ligament; insertion above the ligament may cause a retroperitoneal hemorrhage. A Seldinger technique with careful aseptic technique is recommended for insertion of an arterial catheter, e.g., 3–5 cm polyurethane catheter.[1] The puncture site should be covered with a transparent sterile occlusive dressing and should be regularly inspected. If there is any evidence of impaired circulation in the limb, the catheter should be removed immediately.

Sepsis is more likely to occur if arterial catheters at any site are left in place for more than 5 days [86].

The arterial waveform and the actual pressures obtained from arterial catheters in smaller infants may be affected by the compliance and length of the pressure tubing and by a continuous fluid flush. It is necessary to consider the volume of fluid that is being administered in order to continuously flush the tubing. The use of a pressurized bag with a con-

[1]COOK MEDICAL INC., P.O. Box 4195, Bloomington, IN 47402-4195, USA.

trolled infusion device (e.g., intraflo or squeezeflo[2] system) claims to deliver 3 mL/h of flush solution. However, under some circumstances, it may deliver larger volumes. This may also occur if the rapid flush activator is frequently used or malfunctions [87, 88]. Such circumstances could lead to fluid overload and possible coagulopathy secondary to excessive heparin administration. Cerebral vascular ischemia may occur if the arterial line is flushed with crystalloid solution continuously. This is especially dangerous when using the radial artery, resulting in an ischemic bolus of crystalloid retrograde into the carotid artery after 1.5 mL fluid is injected at bag pump pressures in excess of 200 mmHg [88]. A preferable method to continuously flush arterial lines is to use a syringe pump set [87] to deliver 1 mL/h.

Alternative sites for invasively monitoring arterial pressure have been suggested. The axillary artery is an attractive alternative as it has a very good collateral circulation and it can be easily palpated. It has successfully been used without serious complication in critically ill neonates [89] though secure fixation may be difficult. There are also reports of brachial artery cannulation without serious complication [80], but this must be viewed with caution as this artery has a less well-developed collateral circulation.

Blood pressure is often used as a surrogate measure of organ perfusion, particularly for the CNS and kidney. However, there are no clear data that blood pressure in neonates and young children correlates with outcomes. The quintessential question is, "what is the minimum tolerable pressure before target organ failure results," a question that remains elusive in the neonate. In one study of extremely low birth weight infants, mean arterial pressures (MAPs) <23 mmHg were associated with cerebral dysfunction [90]. The lower target limit of MAP generally increases with both gestational and postnatal age. However, the lower limit of MAP that maintains adequate CBF in the neonate remains to be established [91]. Although multiple factors are likely responsible for cerebral dysfunction after anesthesia, hypotension or inadequate cerebral perfusion has been posited as the factor responsible for the new onset of seizures in six preterm infants who received general anesthesia [92]. All infants underwent radiological investigations, which revealed hypoperfusion in watershed areas of the brain, suggesting a role for hypotension in the pathogenesis of the cerebral dysfunction. On the other hand, treating hypotension with excessively aggressive fluid or vasoactive drug administration may itself result in adverse sequelae such as a patent ductus arteriosus or intracranial hemorrhage. Treatment of hypotension should be prompt but cautious to avoid over-transfusion and hypertension.

[2]ICU Medical Inc., 951 Calle Amanecer – San Clemente, CA 92673, USA.

Definition of Hypotension

There is considerable controversy regarding the definition of the lower limit of an acceptable blood pressure and thus hypotension in neonates and infants. Interest in this issue may shed light on a possible relationship between general anesthesia and neurocognitive sequelae in young infants. Systolic blood pressures at 1 MAC inhalational anesthesia in neonates and infants, measured noninvasively, were reported to decrease 20–30% from awake (baseline) values without surgical stimulation [93, 94]. In 1999, the lower limit for the MAP (measured invasively) for awake, low birth weight neonates on the first postnatal day was determined based on their gestational age (23–35 weeks gestation) and birth weight (500–1500 g). The results indicated that the 95% CI for the lower acceptable MAP in neonates >800 g correlated numerically with the gestational age between 26 and 32 weeks but in neonates <800 g at birth, the lower acceptable MAP was less (Table 7.1a/b) [95]. This 1999 "rule of thumb" was subsequently adopted as the lowest acceptable MAP in anesthetized neonates beyond the first day of life and using noninvasive measurements of blood pressure without evidence. A survey of members of the Society of Pediatric Anesthesia and the Association of Paediatric Anaesthetists of Great Britain and Ireland reported that 87% use the MAP and 72% use systolic blood pressure to define hypotension [96]; median systolic blood pressure definition of hypotension in neonates was 50 mmHg (25th to 75th percentile were 40–60 mmHg) and in infants up to 2 years of age, it was 60 (50–65 mmHg) [92]. A retrospective review of infants <6 months of age reported that neonates displayed the greatest incidence of hypotension (defined as a MAP <35 mmHg) (25%) after induction of anesthesia and they also experienced the greatest incidence of sustained hypotension (>10 min) (44%) compared with the older infants [97].

In 2017, the Pediatric Advanced Life Support and American College of Critical Care Medicine defined shock as a systolic blood pressure <60 mmHg for neonates and <70 mmHg for those ≥2 years of age, although these values bore little relevance to the anesthetized condition (Table 7.2) [98]. For guiding therapy, the minimum perfusion pressure in septic infants was defined as [98]:

$$\mathrm{MAP}\left(55+\mathrm{age}\left(\mathrm{years}\right)\times 1.5\right)\mathrm{mmHg}\left(\mathrm{Table}\ 7.2\right)$$
$$-\left(\text{the central venous or mean arterial abdominal pressure}\right)$$

The recommended MAP was based on the formula for the 50th percentile in the healthy population. According to these guidelines, the minimum MAP in the neonate was 55 mmHg, with a central venous pressure of 0 mmHg [97]. The Multicenter Perioperative Outcome Group constructed reference curves for normal blood pressures in infants and children during induction and maintenance of anesthesia [99]. They extracted blood pressure data from the anesthetic

Table 7.1 (**a**) Lower 95% confidence interval for MAP vs. gestational age

Gestational age (wk)	*23*	*24*	*25*	*26*	*27*	*28*	*29*	*30*	*31*	*32*	*33*	*34*	*35*
MAP (mmHg)													
0-12 h:	20	21	23	23	25	26	27	28	29	30	31	32	33
13-24 h:	20	22	23	25	27	28	29	30	32	33	35	36	37
(**b**) Lower 95% confidence interval for MAP vs. birthweight													
Birthweight (g)	*500*	*600*	*700*	*800*	*900*	*1000*	*1100*	*1200*	*1300*	*1400*	*1500*		
MAP (mmHg)													
0-12 h:	20	21	22	23	24	26	27	28	29	30	31		
13-24 h:	21	22	23	25	26	28	29	30	32	33	34		

Modified from Lee, et al.[91]

Table 7.2 Systolic blood pressure (SBP) of Pediatric Advanced Life Support according to the American College of Critical Care Medicine

Age	SBP (mmHg)
0 day–1 month	<60
1–3 months	<70
3 months–1 year	<70
1–2 years	<70+(2 × age in years)
2–4 years	<70+(2 × age in years)
4–6 years	<70+(2 × age in years)
6–10 years	<70+(2 × age in years)
10–13 years	<90
>13 years	<90

records of 100,000 ASA 1 and 2 children and were developed in conjunction with the World Health Organization growth charts (http://www.pediatric-anesthesia.eu/bp_calculator/) yielded 50th percentile values for the systolic and mean NIBPs under anesthesia for boys of 48 and 33 mmHg, respectively, with large variability in the data [95].

In 2017, a retrospective review of 735 term and 82 preterm infants undergoing laparoscopic pyloromyotomy determined the frequency of hypotension as well as relative and absolute hypotension. They found that, overall, hypotension was greatest in neonates compared with older infants and greater in preterm infants than in full-term infants [100]. Of this cohort, 77% developed relative hypotension (a systolic pressure >20% below preinduction values) and 21% developed absolute hypotension (absolute hypotension defined as a systolic pressure <35 mmHg) primarily during the presurgery and even the surgical periods. These subtle findings helped to focus the results of the Apricot study of serious adverse events in infants and children undergoing anesthesia in Europe [101]. The greatest frequency of both cardiac and respiratory adverse events occurred in infants <1 year of age. It was suggested that this resulted from inadequate training in pediatric anesthesia, a finding confirmed in at least one institution where the frequency of cardiac arrest in infants decreased three-fold when only specialists trained in pediatric anesthesia anesthetized these infants [102]. The final common pathway by which hypotension and cardiac arrest results in long-term cognitive dysfunction is if they are associated with cerebral ischemia. To that end, when cerebral oxygen saturation was measured in 453 infants <6 months of age, a low cerebral oxygen saturation did not correlate closely with a low MAP [103]. Moreover, severely low cerebral oxygen saturation was rare and brief and unlikely to explain neurocognitive dysfunction.

Although it is useful to know the average blood pressure of infants, the optimal target value in any particular neonate must take into account the entire clinical picture to ensure that adequate organ perfusion is maintained. The exact MAP or systolic blood pressure and the duration of exposure to that pressure that is needed to adversely impact neurocognitive function in neonates in the long-term remains undetermined.

Central Venous Pressure Monitoring

CVP monitoring is frequently indicated in order to assess volume status and/or cardiac function. The normal CVP in a ventilated neonate is about 4–6 mmHg. Low CVP pressures, ≤2 mmHg, suggest hypovolemia or dehydration, whereas values >8 mmHg suggest cardiac disease.

CVP lines may also be indicated for the administration of parenteral nutrition fluids and some medications (Fig. 7.9a). In an urgent situation, they may also be used for rapid volume replacement, and only if peripheral IV access is unavailable. It must be emphasized that this fluid is being directed immediately into the heart and electrolyte and temperature differences may trigger arrhythmias. To avoid serious sequelae in such cases (e.g., life-threatening arrhythmias), the fluid (blood or plasma) should be warm, nonacidic, and normokalemic.

Central venous access using ultrasound guidance (USG) has been described in preterm and full-term neonates for the internal jugular vein (IJV), subclavian vein, and brachiocephalic (or innominate) vein (BCV) (Fig. 7.9b, c) [104–110]. Anatomically, cannulation of the BCV at the venous confluence of the internal jugular, subclavian, and brachiocephalic

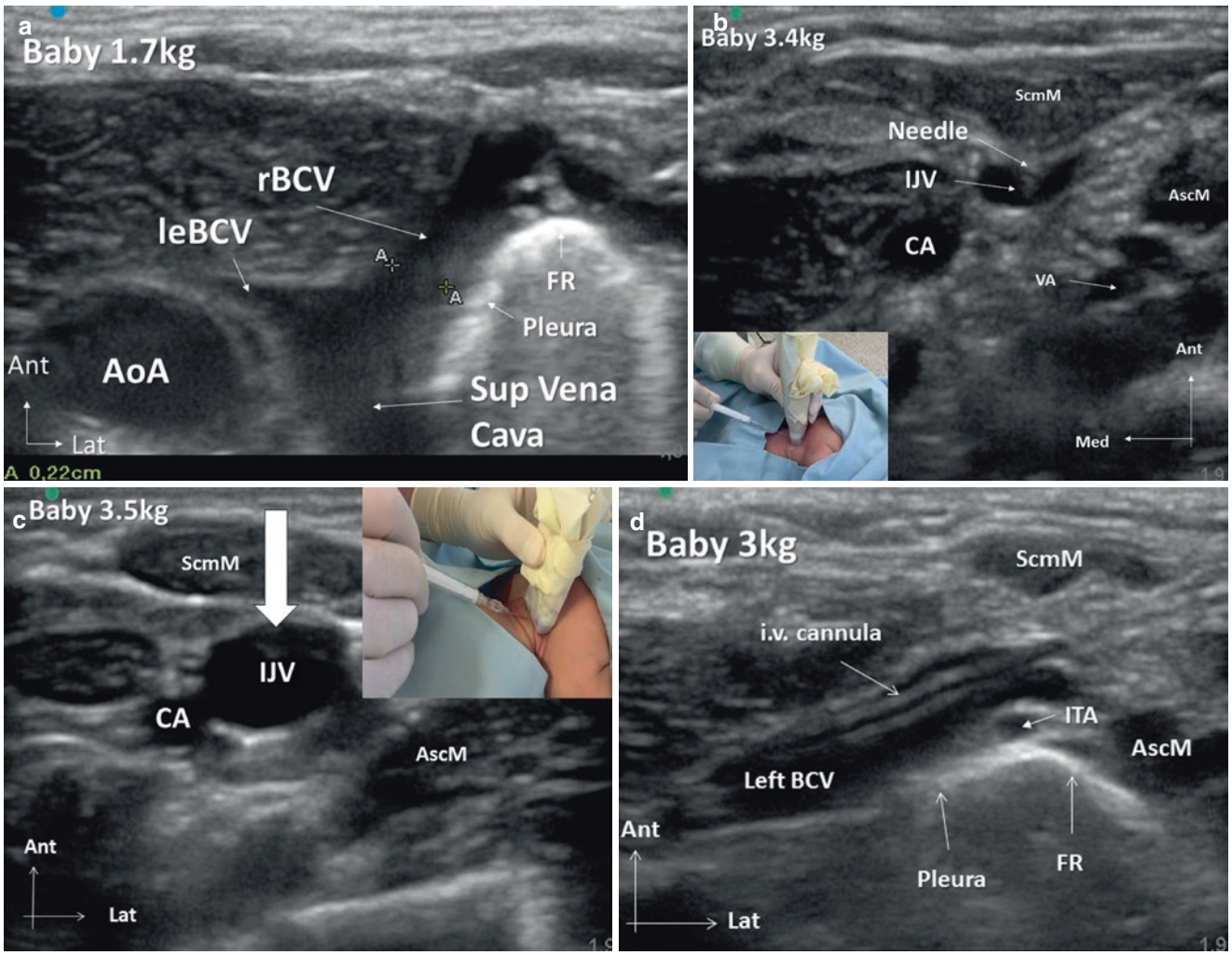

Fig. 7.9 (**a**) Ultrasonographic long-axis view of the right BCV in a 1.7 kg infant. (**b**) Short axis view of the collapsing right internal jugular vein due to puncture needle approach using the out-of-plane technique in a 3.4 kg infant. Ultrasonographic image: *IJV* Internal jugular vein, *CA* Carotid artery, *ScmM* Sternocleidomastoid muscle, *AscM* Anterior scalene muscle, *VA* Vertrebral artery. Small picture: 22-gauge needle with attached syringe aiming at the internal jugular vein via the short axis view. (**c**) Out-of-plane puncture of the right internal jugular vein in a 3.5 kg baby. Ultrasonographic image: *IJV* Internal jugular vein, *CA* Carotid artery, *ScmM* Sternocleidomastoid muscle, *AscM* Anterior scalene muscle. Small picture: 22-gauge needle with attached syringe aiming at the internal jugular vein via the short axis view. (**d**) Ultrasonographic long-axis view of the left BCV in a 3 kg infant with the 22-gauge i.v. cannula clearly inside the vein. Ultrasonographic image: *AscM* Anterior scalene muscle, *FR* First rib; ScmM. (**e**) Brachiocephlic venous catheter fixed on the left shoulder in a 900 g baby. (**f**) Long axis view of the left subclavian vein in a 3.2 kg infant. Ultrasonographic image: *SCV* Subclavian vein, *IJV* Internal jugular vein, *FR* First rib, *ScmM* Sternocleidomastoid muscle. A: diameter of subclavian vein via long axis view: 3.3 mm. B: depth of SCV from the skin surface: 7.7 mm. Small picture: Ultrasound probe placed at the supraclavicular area across the clavicle so as to obtain an optimum long axis view of the left SCV. *Cl* Clavicle; i.v. cannula indicating the in-plane approach to the SCV. (**g**) Ultrasonographic view of the entire long-axis view of the caudally directed right BCV in a 2.1 kg infant. Ultrasonographic image: *AscM* Anterior scalene muscle, *FR* First rib, *ScmM* Sternocleidomastoid muscle, *BCV* Brachiocephalic vein, white, boldfaced arrow indicating the implied i.v. cannula insertion. Small picture: Ultrasound probe placed in the right supraclavicular region so as to obtain the optimum long-axis view of the right BCV. Cl, clavicle; i.v. cannula indicating the in-plane approach to the BCV. (**h**) Out-of-plane puncture of the right BCV via an ultrasound probe placed in the supraclavicular region. Ultrasonographic image: *SCV* Subclavian vein, *Cl* Clavicle. Small picture: Puncture needle aiming at the venous confluence via an out-of-plane approach. *Cl* Clavicle. *Cl* Clavicle. *Ultrasound image*: *rBCV* Right brachiocephalic vein, *leBCV* Left brachiocephalic vein, *AoA* Aortic arch, *FR* First rib, A–A: A, diameter of the right BCV: 2.2 mm

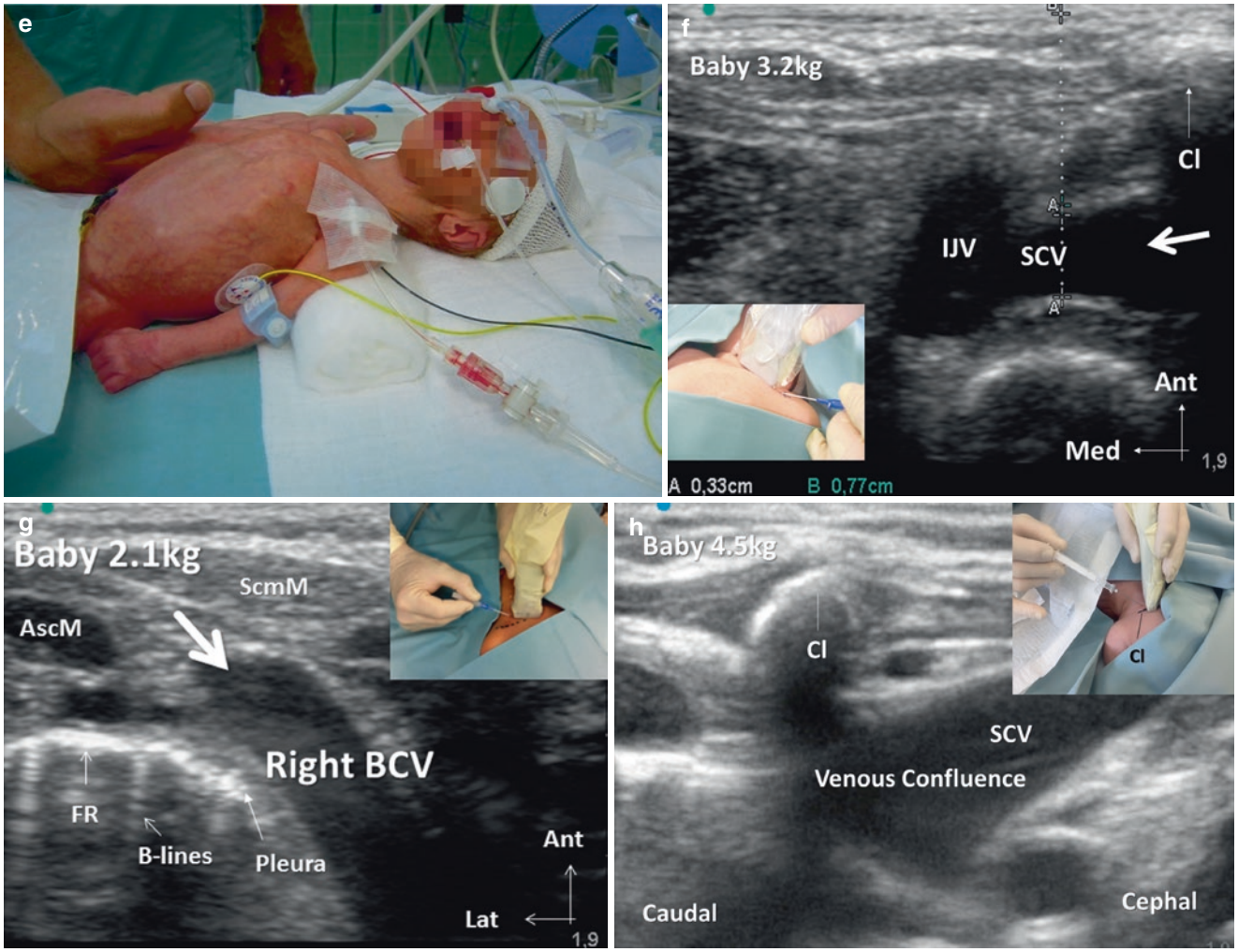

Fig. 7.9 (continued)

(or innominate) veins known as the Pirogoff confluence or the BCV itself are less likely to puncture the pleura (Fig. 7.9d) [110]. The size of the targeted vein should always be determined by ultrasound (US) before cannulation (Fig. 7.9e) [111], inserting a catheter whose outer diameter should be at least one-third smaller than the vessel lumen.

Central venous pressure is commonly monitored via percutaneously inserted internal jugular catheters. The use of USG results in a high success rate for first time catheter insertion even in low birth weight infants. Alternatively, the brachiocephalic vein may also be cannulated using USG.

Cannulation of the Internal Jugular Vein

Transcutaneous insertion of a CVC via the IJV in the neonate has been greatly facilitated by the use of US [105]. The vein is readily recognized by the ease with which it collapses under minimal pressure of the transducer on the neck (Fig. 7.9f). Application of skin traction with tape applied in an upward direction during catheterization will increase the lumen of the IJV and facilitate a successful cannulation [112]. Effects of a combination of Valsalva maneuver, liver compression, and Trendelenburg in infants nominally increases the cross-sectional area of the IJV, 17% [113]; limited effectiveness of the Trendelenburg position in neonates may be attributed to their small length and thus the small vertical distance between the heart and the neck adding very little back pressure on the vein. Rotating the head 40° to the right when canulating the right IJV provides the greatest cross-sectional diameter with less overlap with the carotid artery as 80° [114]. It is, however, common to place a small roll under the shoulders. The diameter of the IJV is larger than that of the subclavian vein and as such is often preferred; in addition, thrombotic events occur less frequently in right-sides central lines and in the IJV compared with the subclavian vein although the IJV is associated with an increased risk of catheter infections (Fig. 7.9g) [115, 116]. The left subclavian vein may also be cannulated, preferably using US to locate the vein accurately [117], which recog-

nizes that its diameter is smaller than the IJV in the neonate [111]. Complications from cannulating the subclavian vein, including pneumothorax, are greater than those from cannulating the IJV. Selecting the correct depth of insertion may be difficult in the smaller infant. The catheter length may be estimated using external measurements of the distance between puncture site and the upper sternum. However, radiological evidence of the optimal depth of insertion should always be noted. The tip of the catheter should not rest inferior to the junction of the superior vena cava with the right atrium confirmed by radiology [117]. If the tip is advanced into the right atrium, serious complications including arrhythmias, damage to the tricuspid valve, or cardiac perforation with cardiac tamponade may ensue.

Cannulating the Brachiocephalic Vein (BCV)

We advocate USG when cannulating the BCV via the supraclavicular approach (Video 7.1) [104, 107, 118]. The US probe should first be positioned to identify the IJV and then shifted caudally to identify the junction with the subclavian vein. The BCV is then identified by tilting the US probe medially. The right is often chosen over the left BCV because of a lower risk of catheter-related thrombotic events in the former, although the left BCV is larger and easier to cannulate (Fig. 7.9a, h) [104, 106, 118]. Given the risk of complications during subclavian and BCV punctures due to the proximity of the veins to the pleura, the IJ route is generally preferred by anesthesiologists.

Central Venous Access: General Principles

Full aseptic precautions should be observed during central venous cannulation in neonates for all approaches. The correct choice of skin prep solutions is important: 10% povidone-iodine solution may affect thyroid function in preterm infants. A solution of 0.5% chlorhexidine gluconate in 70% isopropanol has been recommended as its antibacterial effectiveness is several-fold greater than betadine [119]. When CVCs are used to deliver hyperalimentation solutions, asepsis is obligatory as catheter-related infections and endocarditis are common complications.

When access to the superior vena cava is difficult or impossible, the femoral vein may be cannulated. Pressure in the IVC (i.e., via femoral vein cannulation) accurately reflects the central venous pressure in the atrium [120]. The success rate for this approach is ≥80%, with an arterial cannulation rate that varies between 2 and 12% depending on the size of the preterm infant and a number of other minor complications [121, 122]. Care should be taken when threading the catheter to ensure the tip does not extend too far, entering the veins of the liver, heart, or other organs [122]. The frequency of thrombosis of the femoral vein after cannulation is almost 10 times greater than with a Peripherically Inserted Central Catheter (PICC) line and 4 times greater than with an umbilical vein [123].

The Nervous System

Neurological monitoring in the neonate poses special challenges because the immature central nervous system limits the functional information that can be acquired. However, the well-being of the nervous system depends on protecting it during critical illnesses; thus, it is essential to detect and correct situations that may compromise its functioning. Monitoring of the nervous system involves a multimodal approach integrating electrical activity, CBF, and cerebral oxygenation.

EEG and Amplitude-Integrated EEG (aEEG)

The EEG has been used to monitor brain electrical activity in the neonatal intensive care unit for many years. Standard montages used in adults were simplified from 21 to 9 electrodes to accommodate the smaller head of the neonate. The EEG recording in the neonate varies considerably with gestational and postnatal age. A developmental glossary of EEG in premature and full-term infant was recently published [124], which included a summary of the EEG changes with age [125]. Given its complexity, interpretation of the neonatal EEG requires an experienced technician and a neurologist, effectively limiting the monitoring to only a few hours daily.

Amplitude-integrated EEG (aEEG) was developed in the late 1960s as an alternative tool for continuous EEG monitoring that could be used at the bedside by a trained nurse and a non-neurologist clinician. These changes vastly improved the use of this monitor. The cerebral function monitor, a device using aEEG, was originally developed as a tool to predict outcomes after cardiac arrest in adults [126]. Since the publication of a reference atlas for aEEG in infants in 2003 [127], aEEG has gained popularity in both Europe and North America. aEEG has variable sensitivity and specificity, rendering it unsuitable as the sole diagnostic and management tool for seizures in neonates [124]. Nonetheless, it does effectively screen for seizures in this age group. This approach provided continuous cerebral activity information with minimal interference in patient care [128].

The aEEG signal is predictably altered during general anesthesia and may be used as a depth of anesthesia monitor, while also serving as an important index of cerebral well-being.

The aEEG relies on signals from either a single pair ($P_3 \rightarrow P_4$) of electrodes, or two pairs ($C_3 \rightarrow P_3$, $C_4 \rightarrow P_4$). The central–parietal areas are preferred for monitoring the neonate as this area is at risk for hypoperfusion from the phenomenon of vascular watershed. Frontal locations are not recommended for two channel monitoring as this area is electrophysiologically underdeveloped and seizure activity may not propagate to the frontal region [129].

The aEEG device is portable and designed for ease of use [130]. The signal from the electrodes is amplified, filtered (2–15 Hz bandpass), rectified, and presented as a peak-to-peak voltage. By filtering out signal frequencies in excess of 15 Hz, interference from muscle activity and electrical devices is eliminated. Filtering out frequencies less than 2 Hz removes low-frequency delta waves. Many algorithms weight the alpha over the theta or delta waves although the predominant waves present in the premature neonate are the delta and theta waves. Alpha and beta waves first emerge after 34 weeks of gestation. The aEEG is displayed at slow speeds to reveal trends. Raw EEG can be displayed on the screen so that rapid changes such as seizure activity can be observed [129]. Several commercial devices measure aEEG, but the results can vary depending on the peak detection algorithm [131].

The aEEG displays an upper and lower voltage band. A normal aEEG has a lower voltage >5 μV and an upper voltage >10 μV [131]. An aEEG trace with a lower band ≤5 μV and an upper band >10 μV is moderately abnormal; the combination of lower band <5 μV and upper band <10 μV is defined as severely abnormal or suppressed [132]. An abnormal or suppressed aEEG, when present many hours after birth asphyxia, is predictive (>70%) of death or neurological disability [132–134].

Changes in aEEG voltages occur with decreased cerebral perfusion and decreased cerebral metabolism. For example, decrements in the aEEG amplitude that last 10–20 min were noted in infants given surfactant who experienced a decrease in mean blood pressure and increased pulmonary shunting [135, 136]. Decreased aEEG voltages were also noted in a subgroup of infants undergoing ductus ligation under anesthesia who manifested decreases in mean blood pressure and decreases in the NIRS-measured S_cO_2 [137].

aEEG patterns are related to cerebral perfusion from the first day of life, in both very premature infants and term infants with congenital heart disease [138, 139]. The relationship between aEEG and blood pressure is less clear as abnormal aEEG patterns may not manifest in some infants until the mean arterial pressure is less than 23 mmHg [90]. Additionally, aEEG is not adversely affected by mild hypothermia [140]. However, aEEG output must be scrutinized for artifact from electrical interference, high-frequency ventilator, or ECG interference [141]. Collectively, these data suggest that aEEG may be a useful monitor to assess the adequacy of cerebral perfusion under conditions present in the operating room provided measures are taken to minimize interference.

Neonatal hypoxia–ischemia (H–I) induces significant changes in the coupling between cerebral perfusion, metabolism, and electrical activity [142]. The aEEG pattern (normal, moderately abnormal, suppressed) correlates with changes in CBF and metabolism. Abnormal aEEG is also associated with reduced oxygen consumption in the presence of high-cerebral oxygen saturations (e.g., low fractional oxygen extraction) after birth asphyxia [134]. Abnormal aEEG patterns after neonatal H–I have been associated with decreased glucose utilization as measured by positron emission tomography, whereas normal aEEG patterns have been associated with normal glucose utilization [143]. Cooling is frequently instituted as a means of reducing the likelihood of long-term brain injury in infants, who experience hypoxia–ischemia. Abnormal aEEG patterns do not portend a poor neurological outcome in the presence of systemic hypothermia, unless the patterns persist for more than 36 h [144].

Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is an optical technology based on the relative transparency of biological tissues to near-infrared light (700–900 nm) where oxygen binding chromophores, hemoglobin and cytochrome oxidase, have distinct absorption spectra. Although it is theoretically possible for NIRS to separately determine oxygenation of blood and the cell through hemoglobin and cytochrome oxidase, measurement of cytochrome oxidase distinct from hemoglobin has proven to be difficult. Thus, the application of NIRS in the clinical setting has focused on monitoring hemoglobin oxygenation.

Hemoglobin saturation determined using NIRS differs from that of pulse oximetry in several respects. First, NIRS interrogates hemoglobin mainly in small vessels (arterioles, capillaries, and venules), thereby providing a mixed vascular oxygen saturation of the gas-exchanging circulation, whereas pulse oximetry interrogates hemoglobin in the arterial circulation. Under normal conditions, the NIRS cerebral saturation (ScO_2) is only 60–80% due to the dominance of venous blood in the tissue circulation. During cardiac arrest, ScO_2 decreases as brain tissue consumes oxygen, whereas arterial saturation remains constant or unmeasurable with the poor perfusion during the pulseless state.

Second, NIRS views the large, total signal of photons passing through the tissue to derive ScO_2, whereas pulse oximetry selects the tiny portion of photons passing through the arteries as a pulse-gated signal to calculate SpO_2. In term and preterm neonates, the superficial layers of skin, bone, and cerebrospinal fluid, which constitute a thickness ≤6 mm, do not preclude measurement of tissue oxygen saturation with the NIRS instrument using a model of the brain [145]. During poor perfusion and/or an extremely weak pulse signal, the NIRS readings remain steady and accurate, whereas the pulse oximeter fails to provide an accurate measure of oxygen saturation. Finally, NIRS ScO_2 reflects the balance between oxygen delivery (blood flow, hemoglobin concentration, and arterial saturation) and metabolism (oxygen con-

sumption) and function of the tissue, whereas SpO_2 only reflects oxygen delivery and function of the lungs. Thus, a decrease in ScO_2 may be attributable to a decrease in CBF (resulting from hypotension, hypocarbia, or other causes) [146], arterial saturation, blood hemoglobin concentration, or an increase in cerebral oxygen metabolism, although the decrease usually results from a decrease in CBF or arterial saturation. As such, combining pulse oximetry with NIRS facilitates diagnosis of a pulmonary or CBF problem and the institution of appropriate therapy at the bedside.

It is also possible to measure CBF using NIRS and the Fick equation with oxyhemoglobin or indocyanine green employed as the tracer. Oxyhemoglobin will be an effective if the inspired oxygen concentration is increased by an amount sufficient to increase arterial saturation by at least 5% over 6 s [147, 148]. NIRS can measure CBF by rapidly injecting intravenously indocyanine green, an FDA-approved compound strongly absorbs at 800 nm, as the tracer instead of oxyhemoglobin. Recent advances in theoretical physics and optical technologies have improved the capability of NIRS to measure ScO_2. Before 2008, NIRS devices that measured absolute ScO_2 were research oriented and not commercially viable, and the commercially available NIRS devices could only measure trends in ScO_2, not absolute ScO_2 values. Since that time, Somanetics, CasMed, and Nonin manufacture FDA-approved NIRS devices for neonates, which can determine the absolute ScO_2. Evidence suggests these sensors correlate closely although the absolute ScO_2 may differ by as much as 10–15%, which may complicate the interpretation of clinical studies [149].

What are the critical ScO_2 values that diagnose cerebral hypoxia–ischemia and predict brain damage? In neonatal pigs, cerebral function begins to deteriorate when the ScO_2 decreases to <45%, noted by slowing of EEG and accumulation of tissue lactate. As ScO_2 decreases to less than 35%, cerebral energy fails, expressed by loss of tissue ATP and isoelectric EEG [150]. Given normal values of 60–80% for the ScO_2, a buffer zone of approximately 15% exists during which ScO_2 may decrease before brain function begins to change [151, 152]. The risk of brain damage depends on the severity and duration of the hypoxic–ischemic insult. For insults producing isoelectric EEG and loss of ATP, <30 min of hypoxia–ischemia will inflict brain damage. Consequently, insults that decrease the ScO_2 to <35% require an intervention to restore the ScO_2 within 30 min to reverse the insult. For hypoxia–ischemic insults that cause an ScO_2 between 35 and 45%, the brain will not exhibit evidence of damage for the first 2 h, but thereafter, the risk of brain damage increases 15% for each hour of hypoxia–ischemia [153]. Studies in neonates in the intensive care unit after congenital heart surgery suggest that the risk of brain injury at ScO_2 <45% increases after 3 h [154, 155]. Interventions are warranted within 2–3 h of onset of ScO_2 values at 35–45% to preclude irreversible impairment.

NIRS has been most widely applied for congenital heart surgery in neonates, as well as in addressing the functionality of other organs. In many centers, NIRS has become a standard of care for brain monitoring and somatic oxygen saturation in congenital heart surgery. After balloon septostomy for transposition of the great arteries, NIRS depicted a significant improvement in ScO_2 compared with those that did not undergo septostomy for 24 h [156]. Treatments to increase ScO_2 depend on the type of cardiac malformation. For hypoplastic left-heart syndrome and other similar physiologies, the following will increase the ScO_2: decrease in cerebral oxygen metabolism; administration of inotropes, blood transfusion, or fluid bolus to increase arterial pressure and cardiac output; hypoventilation or ventilation with carbon dioxide to increase arterial PCO_2, CBF, and cardiac output; and ventilation with hypoxic gas to decrease pulmonary blood flow and increase systemic cardiac output [157–159]. Administration of oxygen can increase or decrease ScO_2, depending on the malformation and physiology. For example, with hypoplastic left-heart syndrome, increasing the FiO_2 increases the SaO_2 but decreases PVR, increases PBF, and decreases the systemic and CBF with a net decrease in the ScO_2. In critically ill neonates, NIRS has been applied to the head and flank or abdomen to determine ScO_2, SkO_2 (kidney), SlO_2 (liver), or SgO_2 (gut) to guide ICU treatments or timing of surgery [160, 161]. In neonates undergoing noncardiac surgery, NIRS reported a frequent regional hypoxia (in the cerebral and renal tissues) intraoperatively and postoperatively, two to three times more frequently than pulse oximetry [160]. Moreover, NIRS was effective in detecting postoperative apnea.

NIRS has also been employed during surgery to guide anesthesia and surgical management. Before and after cardiopulmonary bypass, the anesthesiologist uses NIRS to diagnose brain and somatic hypoperfusion and ischemia and guide therapies to restore tissue oxygenation, similar to that in the ICU [152, 157]. During surgery, NIRS displays characteristic changes that may be used to monitor the brain during cardiopulmonary bypass (CPB) [158, 162]. With the institution of CPB, NIRS may be used to verify proper placement of the cannula as ScO_2 should not decrease [163]. During CPB cooling, ScO_2 should increase to >90% to reflect the effect of hypothermia on cerebral O_2 consumption. During hypothermic selective cerebral perfusion or low flow CPB, ScO_2 should not decrease substantially [164]. During reperfusion after deep hypothermic circulatory arrest or selective cerebral perfusion, ScO_2 should increase to >80% to indicate cerebral recirculation. If NIRS does not achieve these values during these situations, the anesthetic and surgical team should search for a reason.

NIRS has also been used as a metric during neonatal resuscitation [165]. In the neonatal ICU it has been used to guide treatment during circulatory failure, ventilator management during respiratory distress syndrome [166], and

during extracorporeal membrane oxygenation for respiratory insufficiency associated with diaphragmatic hernia [141]. Although the role of NIRS in the NICU is still used as a research tool, its clinical application is expanding. For example, NIRS identified those asphyxiated neonates who were at risk of developing brain injury as soon as 10 h after institution of hypothermia treatment and who may sustain disturbed cerebral autoregulation [167, 168]. Evidence is also emerging that the combination of aEEG and NIRS during the 18 and 60 h of cooling after the hypoxic–ischemic insult yields the greatest sensitivity and specificity to predict short-term outcomes [169]. In terms of long-term brain injury after hypoxic–ischemic encephalopathy (HIE), there is evidence that late failure of cerebral autoregulation during hypothermia for brain protection while monitoring mean arterial blood pressure and cerebral oximetry, portended pathologic changes on day 3 of hypothermia treatment [170]. In a large neonatal trial, the long-term benefit from using NIRS in premature infants in the first 72 h after birth to reduce cerebral hypoxia could not be confirmed [171].

NIRS has been used to monitor neonates and infants undergoing major noncardiac surgery [172]. Although mild and moderately low levels of ScO_2 occurred frequently in this large cohort of neonates, severely low levels of ScO_2 were rare, even in the presence of prolonged hypotension. Low mean arterial pressure was common and was not closely associated with low ScO_2. Unrecognized severely low ScO_2 that lasted $\geq$3 min in neonates and infants is less likely to explain the subsequent development of neurocognitive abnormalities than other causes.

Transient bradycardia occurs in preterm neonates in the NICU and during anesthesia. The effect of these heart rate changes on cerebral oxygenation and function is not widely recognized. In fact, 10% of the bradycardias in one study went undetected by pulse oximetry [173]. Moreover, the nadir of tissue oxygen extraction in very preterm neonates was <55% in 61% of those with moderate/severe bradycardia (<50% of baseline or an absolute heart rate <60 bpm) and 35% of those with mild bradycardias (60–80% of baseline). The effect of bradycardia on cerebral oxygenation was more severe in very preterm (26–31 weeks gestation) than in late preterm (32–38 weeks) neonates.

Transcranial Doppler

When sound waves are reflected off a moving object, the frequency of the reflected wave is shifted compared with that of the incident wave; the frequency shift depends on the velocity of the object. If the object is moving toward the sound source, the frequency shift is greater; if the object is moving away from the source, the shift is less. The frequency shift is also referred to as the Doppler shift after Christian Doppler, who described this phenomenon in 1842. Three types of Doppler systems are in clinical use: pulsed wave, continuous wave, and color Doppler. Pulsed wave Doppler allows the user to measure particle velocity up to a limit within a specified region of interest. Continuous wave Doppler has no velocity limit but lacks spatial resolution; the measured velocity is the maximum velocity over the entire beam path. Color Doppler translates information about flow direction and velocity into a color map. Doppler measurements are most accurate when the US beam is directly in line with the moving particles. The measured velocity decreases as the cosine of the angle between the beam and the vector describing the moving particle path.

Both continuous wave and color Doppler instruments have been used to measure CBF velocity in the middle cerebral artery. The continuous wave devices suffer from lack of spatial specificity that can be achieved with pulsed color Doppler techniques. The quality of the measurement can be further improved by obtaining gray scale images so that the optimal probe angle can be determined exactly. US measures of middle cerebral artery blood flow are useful to detect severe cerebral hypoperfusion in infants at risk for hypotension or large ductal shunts, as retrograde or poor diastolic flow occurs in the large arteries near the Circle of Willis in these cases [174]. Normative data for CBF velocity in "healthy" preterm neonates has been published [175]. In non-hypotensive neonates, both systolic and diastolic CBF velocity increases as a function of postnatal and postconceptual age [175].

Conversion of velocity to flow requires knowledge of the arterial cross-sectional area. This measurement is not easily made and is subject to inaccuracies. However, radiographic data suggests that vessel diameter is relatively constant over short periods of time so that changes in velocity are likely to represent real changes in flow. Practical limitations of space and access to probe application sites make application this modality for estimating CBF difficult in the OR environment. There are numerous reports examining the value of Doppler measured CBF before, during and after cardiopulmonary bypass in neonates [176]. In the context of selective cerebral perfusion, low flow cardiopulmonary bypass, and deep hypothermic arrest, transcranial Doppler has been used to detect cerebral hypoperfusion and can guide pump flow rate, surgical and anesthetic therapies intended to prevent cerebral ischemia [176].

Neurophysiological Monitors

The spinal cord and peripheral nerve functions may be monitored during certain operations such as spinal fusion, complex tethered cord releases, and cerebellar–pontine angle tumor resections. This type of monitoring involves measur-

ing the transmission of sensory information from the peripheral nerves to the sensory cortex. Alternatively, the conduction of motor signals from the cortex to the skeletal musculature may be measured, thus assessing the functional state and integrity of motor axons from nerve roots to muscle. These monitoring modalities are known as somatosensory evoked potentials (SSEPs), transcranial motor evoked potentials (TcMEPs), and electromyography (EMG). In our experience, one or more of these modalities may prove useful in selected neonatal procedures.

It is possible to record SSEPs by stimulating the median nerve [177] and/or posterior tibial nerves [178] in preterm and term infants in the awake or lightly sedated state. Neonatal and infant median nerve SSEPs have different morphology and peak latencies compared with those in the adult (Table 7.3). This age difference may be attributable to the degree of myelination and other structural differences between the neonatal and adult peripheral and central nervous systems [179]. In the neonatal ICU setting, both median nerve and posterior tibial nerve SSEPs have prognostic significance for future neurocognitive outcomes in preterm neonates after asphyxia [180, 181]. The cortical SSEP signal is easily obliterated by anesthesia and/or deep sedation in the neonate. However, subcortical recording from Erb's point and the posterior neck are more resistant to anesthetic effects and are of interest when the brachial plexus is the site of the injury. Signals from these structures have been recorded, and normative data for expected latencies has been published [182]. A TIVA technique including propofol and remifentanil produces the least suppression of neurophysiologic signals.

The auditory system of the neonate can be monitored using auditory brainstem responses (ABRs), otherwise called brainstem auditory evoked responses. ABRs are similar to SSEPs in that a nerve (the cochlear nerve) and far-field potentials are recorded. ABRs are obtained by presenting a series of clicks in one ear and a masking noise in the opposite ear, and recording potentials using electrodes placed at each mastoid and one at the vertex of the head. In order to generate an ABR, the recording must be time locked to the stimulus, filtered, amplified many times, and signal-averaged as ABRs have very low amplitude (0.1–0.3 μV), which would be easily overwhelmed by the much greater amplitude EEG signal without special processing.

Table 7.3 SSEP latencies as a function of gestation and age

Gestation/ age	Myelination status of pathways	"N12" latency (ms)	"N 20" latency (ms)
32 weeks	ML–PM TCP–UM		68–72
40 weeks	ML–PM TCP–UM/PM		33–38
6 months	ML–PM TCP–PM	6	18
12 months	ML–FM TCP–PM	6	15.5
3 years	ML–FM TCP–FM	6	15
Adult	ML–FM TCP–FM	13	20–21

ML Medial lemniscus, *TCP* Thalamocortical projections, *UM* Unmyelinated, *PM* Partially myelinated, *FM* Fully myelinated

The ABR from a conscious patient is composed of waves that make up the short, middle, and long latency components of the response. The short latency responses, called Waves I–V, are not easily degraded by sedation and anesthesia. The putative anatomic origin of Waves I, III, and V [183] as well as the latency of each wave differ with age [184]. The structures responsible for the generation of ABR Waves I–V are supplied by branches of the basilar–vertebral system; consequently, the ABR is very sensitive to brainstem ischemia or hypoperfusion [183].

Recognizable and reproducible ipsilateral ABRs can be detected in preterm infants beginning at about 30–32 weeks gestation. Reproducing waveforms can be detected on the contralateral side by 34 weeks gestation. The appearance of wave V on the contralateral side is important, as identification of ABR waves (peaks) is typically achieved by identifying wave V first and working backwards to identify the other waves. In children and adults, wave V is frequently and most clearly seen on the contralateral side as auditory pathways cross the midline at the level of the inferior olivary complex. The neural activation triggered by the clicks used in ABR acquisition travel both ipsilateral and crossed pathways. Recently, the optimal click rate to assess neurodevelopmental outcomes with the ABR in premature infants 34 weeks postmenstrual age was determined to be 29.9/s [185].

The amplitude of the component waves increases with gestational age, whereas the latencies to Waves I, III, and V decrease with gestational age [186]. Analyzing the ABR in premature infants is particularly challenging, although the characteristics of the developing ABR in infants as young as 26 weeks gestation have been reported [187]. The greatest changes in amplitudes and latencies occur after birth. ABR wave amplitudes reach their zenith at 4 years of age and decline slightly to adult values thereafter, whereas latencies reach adult values by about 2–3 years of age (Table 7.4) [184]. ABR wave amplitude is also sensitive to the rate at which the click stimuli are presented [183]. Infants maintain the amplitude of their ABR waves at greater stimulus rates than do adults [186].

ABRs are frequently used to monitor the eighth cranial nerve (CN VIII) and brainstem during neurosurgical procedures involving the cerebellar-pontine angle and posterior fossa tumor resections. Traction on CN VIII, changes in blood flow to CN VIII, or the cochlear nucleus will affect Waves I and II significantly but may also result in loss of

Table 7.4 ABR: change in wave I, II, and V latency with age and wave generators

Gestation/ age	Wave I latency (ms)	Wave III latency (ms)	Wave V latency (ms)
32 weeks	1.6 ± 0.23	4.37 ± 0.27	6.75 ± 0.44
40 weeks	1.6 ± 0.23	4.30 ± 0.25	6.63 ± 0.39
6 months	1.6 ± 0.23	4.06 ± 0.19	6.17 ± 0.27
12 months	1.6 ± 0.23	3.91 ± 0.17	5.91 ± 0.21
3 years	1.6 ± 0.23	3.78 ± 0.16	5.66 ± 0.19
Adult	1.6 ± 0.23	3.78 ± 0.15	5.66 ± 0.17
Generators	Distal cochlear nerve	Olivary complex	Contralateral inferior colliculus

amplitude reduction of all other waves as well. Ischemia in the area of the lateral lemniscus or inferior colliculus will affect wave V. A decrease in amplitude of 50% or more or change in latency of wave V by more than 1 ms may be a sign of brainstem hypoperfusion or insipient ischemia. The ABR is also sensitive to temperature; latency increases about 7% for each 1 °C temperature decrease; and at 26 °C the latencies are double those at 37 °C [188]. ABR amplitude may initially increase as temperature decreases, although hypothermia can obliterate the ABR at 20 °C [188–190].

Special equipment and trained personnel are required for intraoperative interpretation of ABRs. The acquisition time for a single ABR can be on the order of 3–4 min to achieve a reasonable signal-to-noise ratio. However, when available, this modality can provide useful information about the adequacy of brainstem perfusion and auditory pathway function (to level of inferior colliculus). All latency changes must be interpreted in the context of the estimated brain temperature. Inhaled agents, without nitrous oxide, may be used when acquiring ABRs as they are very resistant to anesthesia [191].

TcMEPs are generated by electrically stimulating the motor cortex, either transcranial or directly, and recording the resultant compound muscle action potentials (CMAPs) from various muscle groups. The generation of CMAPs depends on multiple motor neurons innervating a muscle firing in or nearly in synchrony. In order to reach the firing threshold, individual spinal motor neurons must receive a synchronized descending volley of impulses via the corticospinal tract (CST). The conduction velocity of the axons making up the CST of the neonate are much slower and have a large variance compared with those of the adult CST, resulting in temporal dispersion of descending signals [192, 193]. In addition, direct corticospinal to motor neuron synaptic connections are rare in the neonate but increase with age [194]. Under the influence of anesthesia, the motor neurons in a neonate never simultaneously achieve firing threshold in sufficient numbers to record a CMAP after transcranial stimulation. Special stimulation protocols have been devised to partially overcome some of these limitations enabling MEPs to be recorded in infants as young as 2 months postterm [195, 196]. For reasons cited above, the MEPs of very young infants are exquisitely sensitive to anesthesia, thus a propofol–remifentanil-based technique is recommended whenever MEPs are measured for surgical procedures on the spinal cord [191].

Another useful modality for monitoring the integrity of the nervous system is electromyography (EMG). EMG monitors spontaneous muscle activity or stimulated activity. In spontaneous EMG, mechanical or thermal irritation of motor nerves can trigger the release of neurotransmitters at the myoneural junction that generate a muscle action potential. The number of muscle action potentials recorded is a function of the rate of change of the mechanical or thermal stimulus [197]. Rapid warming from electrocautery use, sudden traction, or mechanical trauma can cause a volley of neural discharges that manifests as a burst or train of EMG activity. Conversely, slowly applied mechanical traction does not always result in spontaneous EMG activity, thus stimulated EMG can be used to test nerves at risk of injury.

In stimulated EMG, the surgeon applies an electrical current and looks for a response from one or more muscle groups innervated by a given nerve root. The recording of a CMAP at a low threshold current indicates the structure is a nerve. Motor nerve roots can be stimulated to produce a muscle action potential at very low current levels (<1 mA); the threshold for mixed nerves may be greater (up to 4 mA). Stimulation thresholds obtained while dissecting around nerves fibers or roots can guide surgeons to the distance between the site of dissection and functional neural tissue. EMG is unaffected by choice of anesthetic agents as long as neuromuscular blocking agents are not used. The surgeon may opt to use spontaneous and stimulated EMG recording in an attempt to preserve nerve roots in the neonate, such as during the resection of tumors and other malformations that involve the spine including tethered cord and lipomeningomyelocele, when preservation of neurologic function is expected.

Neuromuscular Junction Monitoring

When non-depolarizing neuromuscular blocking drugs (NMBDs) are used in neonates, the degree of neuromuscular blockade should always be monitored. Such monitoring is especially important during antagonism of blockade and before extubation. This is important for several reasons as given below.

First, acetylcholine receptors are immature in neonates, resulting in an altered response to NMBDs.

Second, the proportion of Type IIb muscular fibers in neonates is significantly greater than in adults. As a consequence, subclinical residual paralysis may persist after antagonism and lead to post-extubation fatigue. It is prudent to document

the extent of muscle recovery after antagonism of the NMBDs in neonates before considering to extubate the trachea. If in doubt, ventilation and sedation should be continued until neuromuscular blockade has been completely antagonized.

However, few anesthesiologists realize that most neonates in NICUs are neither paralyzed during their admission nor are those who return to the NICU partially or completely paralyzed with an NMBD given drugs to antagonize the residual blockade before extubation. For the most part, neonatologists depend on clinical indices to judge the neonate's suitability for extubation, which may result in postoperative respiratory failure, reintubation, and other complications that might have been avoided had the paralysis been antagonized. Two major factors that resulted in a seven-fold increase in the risk of a major respiratory event after extubation following surgery are weight <1.58 kg and postmenstrual age <41 weeks [198]. In our institution, a review of 23 preterm infants determined that of the infants whose paralysis was antagonized, all 12 were extubated successfully within 1 day whereas of the 11 whose paralysis was not antagonized, their tracheas remained intubated for 17 days [199]. It has become our practice to reverse the neuromuscular blockade in all neonates who were paralyzed during surgery before they are discharged from the anesthesiologist's care.

The most commonly used monitor to assess the integrity of the neuromuscular conjunction consists of two electrodes placed to stimulate a motor nerve and elicit a twitch. The possible placements are over the ulnar, facial, or posterior tibial nerves. A train-of-four (TOF) is the commonly used pattern of stimuli over a period of 2 s (2 Hz): the ratio of strength of the first and the last twitch elicited represents the percentage of fibers blocked by NMBDs. A zero response represents full paralysis. It must be recognized, however, that neonates normally exhibit a decreased response to the fourth stimulus. This so-called "Myasthenic response" is due to ACH (acetylcholine) depletion at the pre-junctional site. Hence, in the neonate a ratio of 0.95 may represent a complete return of neuromuscular conduction.

It is also possible to use the neuromuscular monitor to deliver a tetanic stimulation at 50, 100, or 200 Hz. This is accompanied by fade if neuromuscular block is present. Post-tetanic twitches performed after 5 s of tetanic stimulation with a frequency of 1 Hz may demonstrate post-tetanic potentiation but this is less pronounced in neonates than in older patients. These post-tetanic twitches might be performed to detect the depth of paralysis in patients with a lack of any response to TOF stimuli. The tetanic stimulus triggers the synthesis of acetylcholine in the pre-junctional site, delivering the earliest sign of return to muscular function. Post-tetanic stimulation is usually reduced in the neonate due to the immaturity of the pre-junctional ACH production sites.

Temperature Monitoring

Body Temperature Monitoring (see Chap. 8)

Smaller infants are very prone to lose body heat during surgery, the reasons for this are discussed elsewhere. The maintenance of normothermia and avoidance of cold stress will require careful monitoring. However, there are several important considerations to observe: First, there is no uniform "normal" body temperature, different tissues are in different metabolic states, and thus will have different temperatures. Second, the core body temperature may be normal but the infant maintains this while in a state of cold stress [200]. If the objective is to maintain the infant in a thermoneutral state, it is suggested that this may be indicated by a core temperature of 36.7–37.3 °C and a change in core and skin temperature of less than 0.2–0.3 °C/h [201]. These considerations may influence the choice of temperature-monitoring options.

Common sites to monitor the body temperature in the infant are the axilla, rectum, skin, esophagus, and ear.

Measuring the body temperature in the axilla depends upon positioning the probe close to the artery and adducting the arm to close the axillary space, procedures that may not be easily accomplished in the neonate. A warm-air heating device may directly heat an axillary probe tip exposed outside the axillary skinfold. It has also been suggested that active non-shivering thermogenesis may influence readings at this site [200].

Rectal temperature is often considered the best index (Gold Standard) of core temperature, although these readings may be influenced by the depth of insertion of the probe, rectal contents and metabolic activity therein, the temperature of an underlying blanket, and the temperature of blood returning from the lower limbs [202]. It is generally recommended that the probe be gently inserted to a depth of 5 cm [203]. The very rare complication of rectal perforation must be considered [204].

Skin temperature is easily measured and, if this is done with a "zero heat flow" method, it may be preferable to continuous rectal temperature monitoring [205]. The "Zero heat flow" method requires an insulated probe placed on the skin where it rests on the mattress; this achieves zero heat flow and measures the temperature of deep tissues [206].

When measuring the esophageal temperature, it is important to position the probe in the lower esophagus, posterior to the left atrium. This can be achieved by using a combined esophageal stethoscope and temperature sensor and positioning the sensor retrocardiac by auscultating maximum heart sounds through the stethoscope. Temperatures in the upper esophagus may underestimate the true body temperature due to cooling by room air fresh gas flow.

The ear is an unsatisfactory site to monitor temperature in most smaller infants because of the small size of the ear canal. Infrared technology may permit intermittent measurements from the tympanic membrane; this is most often used postoperatively.

Monitoring Blood Glucose

Perioperative hypoglycemia or excessive hyperglycemia should be avoided in the neonate. Intermittent tests using a hand-held glucometer are valuable to confirm normal levels and require very little blood. However, the level of significant hypoglycemia or hyperglycemia in the neonate is at the extremes of the range for reasonable accuracy of hand-held units [207]. Furthermore, the results from glucometers (and other point of care methods) may be affected by alterations in level of oxygenation, hematocrit, or temperature, bilirubin, and drugs such as mannitol or dopamine [207, 208]. An increased hematocrit in the neonate may underestimate glucose readings. Increased PaO_2 levels may underestimate the blood glucose concentration in models using glucose oxidase technology. A new generation of glucometers specifically designed for the neonate with increased reliability will soon be available.

To avoid the obvious disadvantage of intermittent testing, continuous glucose monitoring methods (e.g., Medtronic Minimed, Northridge, CA, USA) to maintain euglycemia have been developed [209]. These devices use a subcutaneous electrode that functions well and are safe even in full-term and preterm neonates [210], despite changes in hematocrit and the use of inotropes. However, they do require frequent calibration against blood samples. The accuracy of these units decreases as hypoglycemic levels are reached, but as this is a continuous monitor, downward trends can be identified early [209]. Continuous glucose monitoring may be useful during neonatal cardiac procedures and may be vital during surgery of a neonatal insulinoma.

Renal Function: Monitoring Urine Output

The vast majority of neonates urinate within the first 48 h after birth: 30% void after birth, 92% void within the first 24 h, and 99% void within the first 48 h [211]. Acute renal failure in the neonate is due to prerenal causes in 75% of cases including hypovolemia, hypotension, increased antidiuretic hormone, and other causes. It is imperative to maintain and monitor an adequate preload in neonates, who require anesthesia and surgery in all but very brief surgical procedures. The use of very low dead-space urine collection tubing and a miniature collecting vessel facilitates accurate monitoring of the small urine volumes [212]. Urine output increases from 6 mL/h in a 20-week fetus to 60 mL/h at 40-week gestation. Important information regarding the fluid status of the patient and/or the onset of impending renal failure may be obtained. Urine flow less than 1.5 mL/kg/h should be considered as a warning of a less-than-optimal state although it is important to remember that neonates may not produce urine in the first 24 h or so after birth [213].

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8 Metabolic Care of the Preterm and Term Infants, Including Control of Body Temperature

Gianluca Bertolizio, Pablo Ingelmo, and Jerrold Lerman

Key Definitions

A full-term neonate is a fetus that has reached ≥37 weeks gestational age at birth, whereas a preterm neonate is <37 weeks gestation at birth. Ninety percent of births are full-term, only ~10% are preterm. Preterm neonates are further divided into early preterm (~2.7% of all births), those born <34 weeks, and late preterm infants (7% of all births), those born between 34 and <37 weeks [1]. Each group carries with its morbidity and mortality risks [2]. Small for gestational age (SGA) infants, which comprise 2–10% of US births, is defined as being smaller than their expected weight (<10%ile for gestational age or <2 standard deviations below the norm) or heel-to-crown length when measured either in utero or as a neonate [3, 4]. Risk factors for having an SGA infant include maternal factors, maternal medical history, and pregnancy history. In contrast, intrauterine growth restriction (IUGR), ~10% of US births, is defined as a neonate that has deviated from the normal intrauterine growth curve often as a result of malnutrition and/or in utero growth compromise [5]. IUGR falls into two broad categories [6]: type 1 or asymmetric, which accounts for 70–80% of IUGR, is referred to as "head-sparing" and has been attributed to uteroplacental insufficiency during the third trimester; and type 2 or symmetric, which accounts for 20–30%, begins in early pregnancy, possibly due to genetics or infection and carries a much worse prognosis. IUGR causes serious perinatal morbidity and mortality ranging from difficult cardiorespiratory transition to metabolic and neurodevelopmental sequelae [7]. Overall, the causes of IUGR are numerous but can be classified into maternal, fetal, and placental or a combination of these [6]. Healthy neonates are also grouped according to their birth weight. Moderately low birth weight (1500–2500 g) neonates occur in 6.9% of births [1]. Very low birth weight (VLBW) neonates defined as a weight of 1000–1500 g occur in 1.4% of births, and extremely low birth weight (ELBW) neonates defined as a weight of <1000 g at birth.

In the early postnatal period (for term and preterm neonates), an initial but transient decrease in urine output (from 12 to 48 h) is followed by a diuresis (excretion of water) and natriuresis (excretion of sodium) defined by a urine output >80% of the IV input [8]. By the 5th postnatal day, urine output stabilized and varied with the fluid intake.

Neonatal Body Water Distribution and Metabolism

At the time of delivery, programmed changes in the cardiorespiratory system bridge life from the fetal to extrauterine world. With birth, the first few breaths rapidly expand the lungs and decrease the pulmonary vascular resistance. The net effect is an increase in pulmonary venous return to the left atrium, which stretches the atrial walls (Fig. 8.1). As the umbilical cord is clamped and the placenta removed from the circulation, systemic vascular resistance also increases, applying strain on the left ventricle. Together, the atrial stretch and ventricular strain increase atrial natriuretic peptide (ANP) levels, which dilate the renal vasculature and promote an initial natriuresis [9, 10]. Although the posterior pituitary gland secretes antidiuretic hormone (ADH) during the early transition to extrauterine life, aquaporin-2 (AQP2), the primary target of ADH in the kidney, is not expressed in the early postnatal period, limiting the urinary concentrating capacity of the kidney, particularly in preterm infants [11]. Despite an intact renin–angiotensin system with normal/high aldosterone levels, sensitivity to aldosterone is also limited, further enhancing the natriuresis. Ductal steal (a *left*-to-*right* shunt across a patent ductus arteriosus (PDA)) decreases renal perfusion, which increases renovascular resistance and

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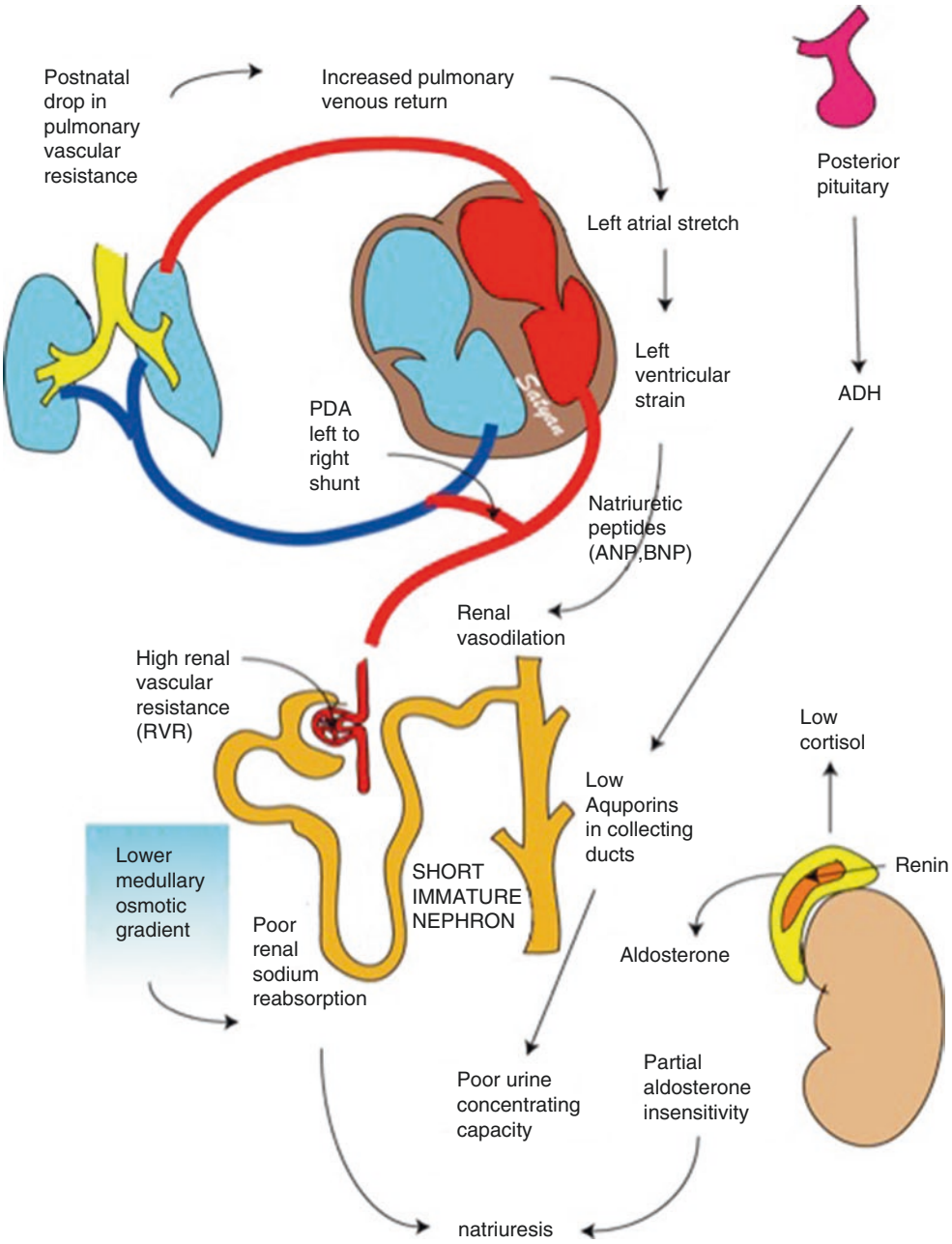

Fig. 8.1 Changes in fluid homeostasis and regulation in neonates (especially preterm neonates) lead to poor concentrating capacity and urinary loss of sodium. Reduction in pulmonary vascular resistance after birth increases pulmonary venous return to the left atrium, thereby stretching the atrium. Umbilical cord clamping and removal of the placenta increases systemic vascular resistance and left ventricular strain. Atrial stretch and ventricular strain increase natriuretic peptide levels, which cause renal vasodilation and natriuresis. Although ADH secretion is present, reduced aquaporins in the collecting duct limit the urinary concentrating capacity, particularly in premature infants. Although the renin–angiotensin system is functional with normal/high aldosterone levels, partial aldosterone insensitivity results in a natriuresis. Ductal steal (left-to-right shunt across a patent ductus arteriosus—PDA reduces renal perfusion), increased renal vascular resistance, reduced medullary osmotic gradient, short immature nephrons, and reduced cortisol concentrations act in concert to limit the ability of the preterm infant to conserve sodium and water

reduces the medullary osmotic gradient. With short, immature nephrons and reduced cortisol concentrations, the ability of the preterm kidney to conserve sodium and water is severely compromised (Fig. 8.1).

Major shifts in fluid homeostasis and regulation occur in neonates and preterm neonates, with immersion into extrauterine life. Distribution of total body water as well as the distribution of water between the extra- and intracellular compartments change dramatically throughout gestation and continue to change through the first 9 months of postnatal life (Fig. 8.2). Total body water comprises 85% of the body weight in the preterm neonate, 75% in the full-term neonate, and then decreases to 60% in older children and adults (Fig. 8.2) [12, 13].

The net decrease in total body water begins slowly postnatally, with limited urine output (oliguric phase) during the first 24–48 h, followed by a diuresis as described below [8, 14, 15]. The early oliguric phase is explained physiologically by low blood pressure, renal blood flow, and glomerular filtration rate (GFR). This oliguric phase is marked by a diminution in urine output to 0.5–1.5 mL/kg/h that lasts 12–36 h. Urine and stool outputs are scant; although >92% of preterm and term neonates pass their first urine and stool outputs by 24–48 h [14]. If the neonate remains oliguric or anuric beyond 36–48 h postnatally, congenital urological or gastrointestinal anomalies should be sought, particularly if cardiorespiratory variables and/or laboratory indices are abnormal

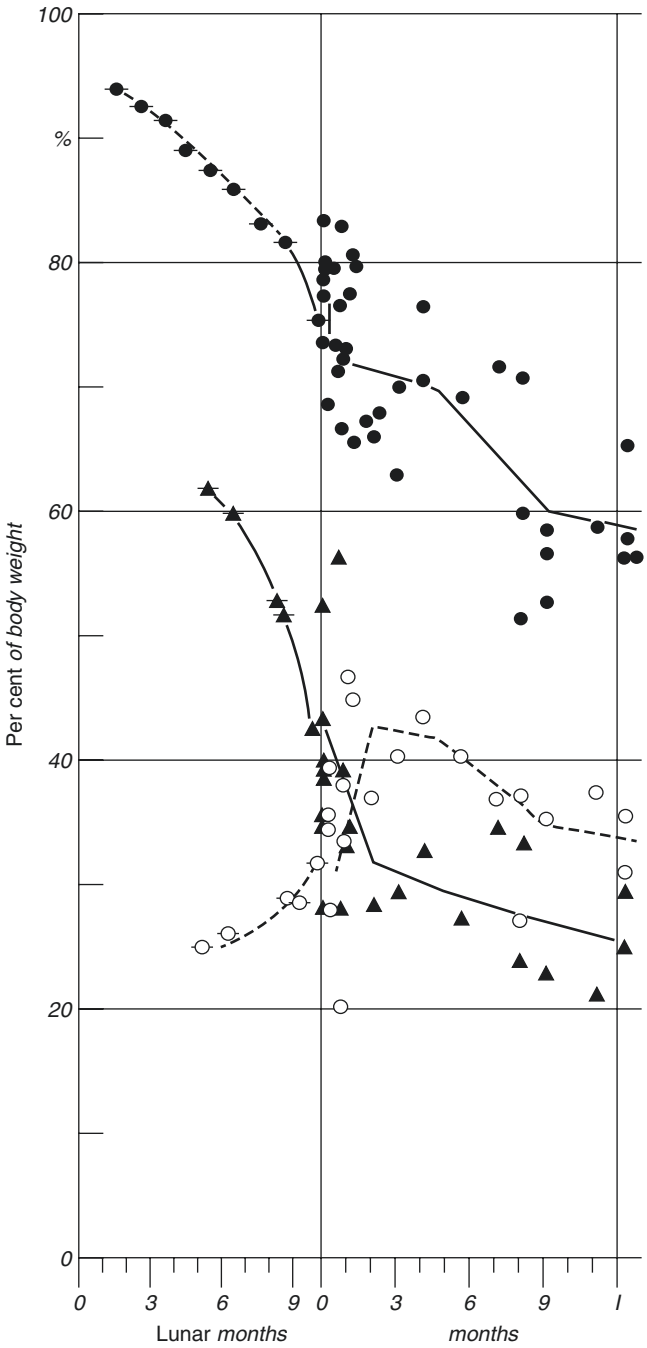

Fig. 8.2 Body water compartment changes during growth (used with permission from FriisHansen B. Changes in body water compartments during growth. In: Linneweh F, editor. Die Physiologische Entwicklung des Kindes. Berlin, Germany. Springer-Verlag. 1959)

[16]. Once the diuretic phase begins, both diuresis and natriuresis occur with a tripling of urine output to 3–5 mL/kg/h for several days, accompanied by a total body weight loss that is independent of fluid intake. The onset of the diuresis has been attributed to an increase in GFR and ANP [17, 18].

A total body weight loss of 5–7% can be expected during these first 5–7 postnatal days, although weight loss in ELBW neonates may be much greater, reaching 10–15% [15]. Weight loss can be attributed, in part, to both sensible and insensible water losses: (1) sensible fluid losses induced by (a) upregulation of ANP secondary to increased pulmonary blood flow and stretch of left atrial receptors during the transition to extrauterine life, (b) tubular insensitivity to aldosterone, and (c) stool losses that comprise about 7 mL/kg/day in preterm infants and 10 mL/kg/day in term neonates; and (2) insensible fluid losses are 10–15 times greater in 24-week preterm infants than in term neonates during the first 24 h [9, 15, 19]. Thereafter, insensible fluid losses continue through the first postnatal month and then decrease, such that the difference between term and preterm neonates dwindles to 2-fold at the end of the first month.

Postnatal Changes in Hypothalamic, Endocrine, and Renal Physiology

Hypothalamic–Pituitary–Adrenal Axis

The adrenal gland is essential for organ growth and maturation both in utero and ex utero. Maturation of the HPA–adrenal gland and its ability to address stress in the fetus and neonate are determined by two developmentally separate hormone drivers: corticotropin-releasing hormone (CRH) and adrenocorticotropic hormone (ACTH). These two drivers inhibit the developing adrenal gland differently and explain why both term and preterm neonates may be unable to cope with stress.

CRH is produced by both the fetal hypothalamus the placenta in utero [20]. The placental source of CRH increases throughout gestation, stimulating the release of cortisol in the fetus. However, in contrast to the hypothalamic source of CRH, the placental source of CRH is not under a negative feedback loop but rather a positive feedback loop such that both CRH and cortisol levels in the fetus increase relentlessly throughout gestation until reaching maximum levels at term [20]. These increased CRH and cortisol levels reset the setpoints in the HPA and adrenal gland in the fetus, so that when the placenta is removed and both CRH and cortisol levels decrease precipitously, the HPA and adrenal glands are relatively insensitive to the decreased CRH and ACTH levels, and unable to mount an appropriate stress response for several days, leaving the stressed term neonate with transient adrenal insufficiency and circulatory instability. In most neonates, this transient period of adrenal insufficiency is unnoticed; however, in those who incur stress at birth, this deficiency may prove to be a challenge to treat.

In the preterm infant, the function of the adrenal cortex and release cortisol varies with gestational age [21]: before 30 weeks gestation, the response of the adrenal cortex to exogenous ACTH is muted. Before 30 weeks gestation, the fetus is unable to synthesize cortisol due to immature enzymes and relies primarily upon placental transfer of maternal cortisol as

its source of cortisol [20]. This maternal source of cortisol suppresses the HPA axis, delaying maturation and in some cases, causing involution of the fetal adrenal gland, which may explain the inability of the ELBW neonate and the neonate with IUGR to respond effectively to stress in the peripartum period including developing respiratory distress syndrome, immaturity of the lungs, and persistent hypotension of the early preterm infant [22, 23]. This occurs because the activity of 11β-hydroxysteroid dehydrogenase type 2 in the placenta is very low in early gestation, permitting maternal cortisol to cross the placenta, but as the fetus matures, the activity of the dehydrogenase type 2 increases, converting the maternal cortisol to cortisone before it reaches the fetus. With the suppression of the fetal HPA waning around 30–33 weeks, fetal ACTH begins to stimulate the adrenal cortex to secrete cortisol. Beyond 33 weeks gestation, the adrenal gland and its functionality mature in parallel with gestational age, so that by term, two-thirds of the circulating cortisol originates from fetal adrenal glands and one-third from maternal sources and placental transfer [21, 24]. However, only 27% of ELBW infants and critically ill neonates are unable to triple their cortisol production rate in response to stress (transient adrenal insufficiency of prematurity) [25]. This early relatively adrenal insufficiency in VLBW neonates may explain, in part, the persistent hypotension and cardiovascular instability in some preterm infants, who are refractory to fluids and inotropes [25–27] but responsive to ACTH and/or steroid therapy during the first 15 postnatal days [20, 22, 27, 28]. Thereafter, the adrenal gland stabilizes cortisol production and this issue dissipates. The stress response in most preterm neonates >30 weeks gestation is also directly related to urinary cortisol levels [22].

In full-term and late preterm neonates, maximum cortisol levels (4–5 times normal) are achieved during parturition and in the first few postnatal hours [24]. Low cord concentrations of ACTH, cortisol, and free triiodothyronine postnatally may be associated with retention of lung fluid and transient tachypnea of the newborn [29]. Moreover, most neonates whose cortisol plasma concentrations are suppressed at birth experience an increase in plasma concentrations within the first 2 postnatal weeks [22].

Ex utero, cortisol holds important roles in maintaining blood glucose and electrolyte concentrations, free water excretion by the kidney, cardiovascular homeostasis, and vascular integrity in the presence of a systemic inflammatory response. In terms of cardiovascular homeostasis, cortisol modulates the activity of beta receptors and their sensitivity to catecholamines, nitric oxide synthase, and calcium flux.

Renin–Angiotensin–Aldosterone

Synthesis of aldosterone in the fetal adrenal gland commences by the 13th gestational week and increases steadily throughout gestation, often exceeding maternal concentrations at birth. The activity of the renin–angiotensin–aldosterone (RAA) system is inversely related to gestational age. Urinary excretion of aldosterone increases significantly in late gestation, between 30 and 41 weeks [19]. In VLBW infants, the production of aldosterone and expression of renal mineralocorticoid receptors [30] are reduced compared with that in full-term neonates predisposing VLBW infants to an increased risk of hyponatremia and dehydration. As aldosterone concentrations increase with gestational age, distal tubular reabsorption of sodium increases, but even by term, healthy neonates exhibit partial albeit transient, tubular unresponsiveness to aldosterone, resulting in an impaired ability to excrete large or acute sodium loads [19]. In fact, at term, plasma concentrations of aldosterone and renin are increased compared with maternal values, despite the associated hyponatremia, hyperkalemia, and urinary sodium loss [31]. The renin–angiotensin system is very active in the first postnatal week, leading to increases in peripheral vascular tone and plasma concentrations of aldosterone [31]. The increase in angiotensinogen and plasma renin activity concentrations has been attributed to the low systemic blood pressure, renal blood flow, and serum sodium concentration, as well as a decrease in extracellular fluid (ECF) after birth.

Aldosterone concentrations and the distal tubular responses to aldosterone normalize as renal function matures by the end of the first year of life.

Atrial Natriuretic Peptides (ANPs)

ANPs attenuate the renin–angiotensin–aldosterone axis and suppress vasopressin (ADH) release. These peptides vasodilate the systemic, pulmonary, coronary, and renal circulations, and promote natriuresis and diuresis [17, 32]. As stated, ANP increases in response to dilation of the atrial walls and ventricular strain during the transition to extrauterine life. This suppresses ADH, aldosterone, and renin; vasodilates the pulmonary and systemic vasculatures; and lastly promotes diuresis and natriuresis. In aggregate, these combine to decrease the extracellular and pulmonary fluid and the ANP concentrations.

The time course of circulating ANP in the peripartum period is one in which the concentration during the antepartum period is small but increases in term neonate (and even greater in the preterm neonate), with the transition to extrauterine life as described above. The concentration of ANP peaks by 2–4 postnatal days and then gradually wanes to reach adults levels between 2 weeks and 2 months postnatally. In children with congenital heart disease, ANP levels vary with the type and severity of the specific heart defect [33].

Antidiuretic Hormone

Antidiuretic hormone (arginine vasopressin (AVP), ADH) increases at the time of delivery, especially in neonates delivered vaginally [34]. ADH secretion increases in response to stress, such as during birth, asphyxia with respiratory distress syndrome (RDS), positive pressure ventilation, pneumothorax, intracranial hemorrhage, and other factors (see Table 8.1). Sensitivity of the volume receptors and osmoreceptors in neonates is similar to that in adults, although the tubular sensitivity to ADH is reduced in preterm infants [36, 37], which augments the excretion of hypotonic urine (see below), an effect that continues postnatally for a brief period.

In utero, the renal response to ADH is attenuated because prostaglandin E2 signals the prostaglandin EP3 receptor to inhibit adenyl cyclase activation, thereby blunting the responsiveness of the collecting duct to ADH [38]. This results in hypotonic amniotic fluid. However, postnatally this function becomes superfluous as prostaglandin levels decrease and ADH is no longer inhibited from binding to the V2 receptor on the basolateral membrane of the collecting ducts. ADH binding to V2 receptors upregulates AQP2 receptors, allowing those water channels to insert into the apical basement membrane of the renal tubule, increasing the permeability of water from the collecting tubules into the cell membranes (Fig. 8.3) [38–40]. AQP2 levels continue to increase steadily, reaching a peak by the 10th postnatal week. Expression of AQP2 is also enhanced by glucocorticoid administration. In preterm neonates, AQPs expression is reduced at birth, peaks on postnatal day 3, and returns to the concentrations at birth by day 7 [41]. AQP3 and AQP4, which also exist in the basement membrane of the collecting tubules, facilitate the passage of water out of the membrane cells and into the interstitium, but likely play a minor role in modulating the egress of water from the collecting tubules. They are not upregulated postnatally.

Table 8.1 Perioperative causes of Increased ADH release

Non-osmotic	Osmotic
Pain	Fasting
Inflammation	Hypovolemia
Stress, catecholamines	Hypertonicity
Surgery; laparoscopic surgery	Hypotension
Vomitting	Renal insufficiency Hypoxia
Hypoxia	Hepatic insufficiency
Hypercapnia	
Medications (e.g., opioids, amiodarone, vincristine)	
Respiratory diseases (e.g., asthma, pneumonia, atelectasis)	
Central nervous system disorders (e.g., head injury, tumors)	

Ref. [35] with permission

Neonatal Renal Function

In the neonate, renal function is quite immature compared with that in the older infant. The number of nephrons in the fetus reaches adult numbers by 34–36 weeks gestation, although the nephrons are shorter and functionally immature [40]. Renal function and the control of fluids and electrolytes are thus impaired in preterm infants <35 weeks postmenstrual age with both fewer and immature nephrons. Postnatal renal maturation, however, is more a function of postnatal age than gestational age. After birth, renal blood flow (RBF) increases in response to the increased systemic blood pressure with a doubling in the GFR during the first 24 h of postnatal life [42]. The increase in RBF is further augmented by closure of the PDA, which is a low pressure siphon of blood away from the systemic circulation to the pulmonary vasculature. However, the kidney in the neonate is less efficient at excreting an acute sodium or water load than the kidney of an older infant or child due to the immature responses to aldosterone and ADH, in addition to incomplete receptor expression. SGA infants are at increased risk for renal insufficiency [43, 44]. The ability of the postnatal kidney to concentrate urine depends on the increased sensitivity of the AQPs to ADH, the level of maturity of the Loop of Henle, and the tonicity of the medullary interstitium.

Neonates tolerate fluid restriction poorly and become dehydrated rapidly as a result of large insensible fluid losses and the inability of the kidneys to concentrate urine. Factors that contribute to this inability to concentrate urine include a decrease in medullary osmotic gradient and a reduced water permeability response of the collecting duct to ADH. The lack of a renal medulla osmotic gradient and the absence of medullary tubules limit the urinary concentrating capacity of the neonatal kidney (600 mOsm/kg in preterm infants and 800 mOsm/kg in full-term neonates) to about half that of adult values (1200–1400 mOsm/kg).

Renal Blood Flow (RBF)

In both preterm and full-term neonates, RBF is reduced at birth primarily because the oxygen tension is reduced and the renal vascular resistance is increased, the latter attributable to upregulation of the renin–angiotensin system. Upregulation of the renin–angiotensin system is key to nephrogenesis as angiotensin II is a potent growth factor for the kidney and vasodilator of the efferent arteriole, which augments the GFR [18, 38]. Nephrogenesis is complete in term neonates, but incomplete in preterm infants <34 weeks gestation, resulting in reduced GFR at birth. In addition, angiotensin II vasoconstricts the efferent arterioles and combines with prostaglandin EP2 and prostacyclin to vasodilate

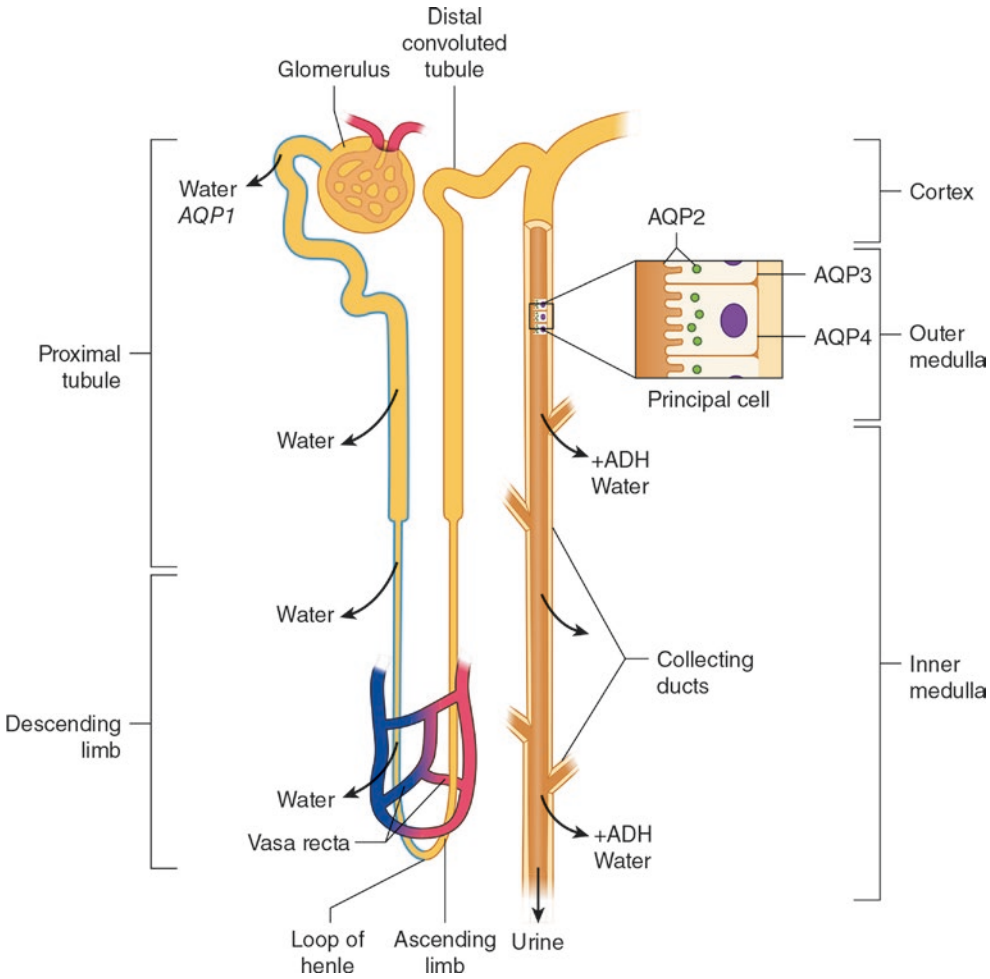

Fig. 8.3 Aquaporin (AQP) in the human kidney. Modified with permission from Ref. [39]

the afferent arterioles to create suitable conditions for the immature kidney to produce glomerular filtrate. Renal vascular resistance is inversely related to gestational age and decreases gradually postnatally, although it exceeds that in adults. RBF increases throughout infancy, reaching adult rates by 2 years of age [38].

During the first 12 h after birth, 4–6% of the cardiac output perfuses the kidney. Renal perfusion increases to 8–10% of the cardiac output during the first week, compared with 25% in adults [38]. A similar pattern of increases in renal blood flow occurs in preterm infants older than 34–35 weeks gestation, with a more gradual decrease in renal vascular resistance and a more gradual increase in GFR [45]. In infants, a greater proportion of RBF perfuses the juxtaglomerular (medullary) nephrons instead of the cortical areas, whereas in adults, the majority of RBF perfuses the cortical area and only 10% perfuses the medullary area. Because the juxtaglomerular nephrons are more involved in the conservation rather than excretion of sodium, this helps to explain the limited ability of the infant to excrete a sodium load.

Glomerular Filtration Rate (GFR)

Although the glomeruli and nephrons are anatomically complete in the term neonate, they are functionally immature, with reduced GFR and the concentrating ability. The GFR in the term neonate is only 25–30% of that in the adult, after adjusting for differences in size and surface area. The reduced GFR in the neonate can be attributed to the small surface area of the glomerular basement membrane, which limits the amount of fluid that can be filtered [40]. This impairs the neonate's ability to excrete a water load. The GFR depends directly on the gestational age; in preterm neonates, the GFR is reduced but increases slowly compared with that in full-term neonates. At 40 weeks postmenstrual age, the GFR is 1.5 mL/kg/min (20–40 mL/min/1.73 m^2), increasing to adult rates of 2.0 mL/kg/min (120 mL/min/1.73 m^2) by 2 years of age. In ELBW infants, the GFR remains reduced until a full complement of nephrons has developed at 35 weeks. The GFR doubles in the first 24 h postnatally, continuing to increase four-fold through the first 2 years of life before reaching the adult rate.

Tubular Function

Despite a full complement of tubules by 34 weeks gestation, proximal tubular resorption in the term neonate lags behind that in the adult [46]. Indeed, renal tubular function reaches adult levels by 1 year of age. Resorption of solutes such as organic solutes, glucose, and bicarbonate occurs extensively in the proximal tubule primarily with the help of active transport. Resorption of sodium occurs via the Na^+K^+ ATPase transporter [47]. Na^+K^+ ATPase activity is decreased in the neonate, along with smaller tubular resorptive surface area, fewer solute transporters, and altered control of H^+ transport compared with older infants. For example, $Na^{+-}K^+$ ATPase activity increases 5–-10-fold postnatally, resulting in resorption of most sodium filtered by the glomerulus through the proximal tubule. Most other secretory and absorptive tubular processes, although immature, are relatively well-developed by term. Along with the solutes, water follows the osmotic gradient via AQP1 channels out of the tubule to ensure isoosmolarity throughout the extra- and intracellular fluid compartments in the body (see below).

The ascending loop of Henle confers a special role in creating hypo-osmolar urine. The ascending loop reabsorbs 25% of the filtered sodium chloride but is impermeable to water, resulting in a hypo-osmolar urine. Although transporters for solutes including sodium are immature, the neonate excretes hypo-osmolar urine at term, with an osmolality as low as 50 mOsm/kg, similar to that of adults [46]. The sodium transporter in this section of the tubule is blocked by diuretics such as Lasix. In contrast to the ascending loop, the distal convoluted tubules resorb ≤10% of the sodium in the glomerular filtrate. However, in similarity with the ascending loop, the distal convoluted tubule is impervious to water. Thus, sodium, potassium, magnesium, chloride, and several other ions are actively resorbed from the ascending loop tubule, further reducing the osmolality of the filtered urine [46].

ADH is upregulated in the presence of an increase in serum osmolarity and hypovolemia [46]. It acts directly on the collecting ducts to resorb free water and increase the osmolarity of the filtrate. The minimum urine osmolarity in both neonates and adults is 50 mOsm/kg, reflecting the ability of the kidney to excrete free water. However, at the other extreme, the neonate is severely restricted compared with the adult, with a maximum osmolarity of 500–700 mOsm/kg in neonates, one-half that in adults, 1200–1400 mOsm/kg.

Infants maximize their urine concentrating ability by 1 year of age. Glycosuria and aminoaciduria are commonly detected in neonates (and in preterm infants in particular) because of immature active transport pumps in the proximal tubule. The rate-limiting step in the neonate's ability to concentrate urine is the failure of ADH to upregulate AQP2 peptides and incorporate them into the basement member of the collecting duct to facilitate the resorption of water.

Aquaporin Peptides

A full description of the role of AQPs in the kidney is beyond the scope of this book. However, in brief, 13 AQPs have been identified in mammals, of which only 4, AQP1–4, are expressed in the human kidney (Fig. 8.3) [39]. These transmembrane protein tetramers consist of four water hourglass-shaped channels that are lined with charged moieties to limit the transit of most molecules, except water [15]. These bidirectional pores allow the passage of water, along osmotic or concentration gradients in the kidney [48]. AQP1, which has been detected in the human fetus by 24 weeks gestation, is primarily found in the apical and basolateral membranes of the proximal tubule and the descending loop of Henle, as well as in the Vasa recta. AQP1 facilitates the resorption of a majority of the water from the glomerular filtrate into the vasculature (Fig 8.3). AQP2 is the second most common AQP in the human kidney, which is found primarily in the collecting duct, apical membranes of storage vesicles, and principal cells. ADH-activated V2 receptors in the principal cells in the ducts activate exocytosis of the AQP2-containing vesicles and their subsequent incorporation into the apical cell wall to resorb water in the collecting duct region of the renal medulla, thereby concentrating the urine. Pathological conditions such as congestive heart failure, in which ADH is upregulated and AQP2 expression is increased, result in increased water resorption from the collecting ducts [48]. The expression of AQP2 in the fetal kidney is limited, even during the latter half of gestation, which is consistent with the limited ability of the neonate to concentrate urine [39]. Water is resorbed from the collecting ducts via AQP2 into the cells and exits into the interstitium via AQP3 and AQP4 channels. AQP3 and AQP4 in the human kidney have not been fully described.

Maintenance Fluid Therapy

Water Requirement

Normal fluid requirements vary markedly in both low birth weight and full-term neonates, as well as throughout infancy (Table 8.2). This variability has been attributed to differences in caloric expenditures, growth rate, evaporative losses, and progress of renal function maturation and proportion of total body water at different ages [50]. Full-term neonates require 60 mL/kg/day of fluid on day 1, with requirements increasing steadily to 150 mL/kg/day by 1 week postnatally [51]. Preterm neonates have larger surface areas relative to their body weights, less subcutaneous fat, and greater insensible water losses than full-term neonates [15, 51]. In the case of VLBW infants, their surface area-to-weight ratios are approximately three times greater

Table 8.2 Average fluid requirements of LBW infants (mL/kg/day) during the first postnatal week [49]

Postnatal days	Source of water loss	Body weight (g)			
		750–1000	1001–1250	1251–1500	1501–2000
1	IWL	65	55	40	30
	Urine	20	20	30	30
	Total	85	75	70	60
2–3	IWL	65	55	40	30
	Urine/stool	40	40	40	45
	Total	105	95	80	75
4–7	IWL	65	55	40	30
	Urine/stool	65	65	65	65
	Total	130	120	105	95

IWL Insensible water loss, *LBW* Low birth weight

than those in full-term neonates, resulting in greater insensible fluid losses. These losses, combined with the greater urinary excretion of solutes and reduced tubular concentrating ability, further increase the obligatory fluid losses in these neonates [51]. Under normal conditions, a Cochrane review concluded that careful water restriction to maintain normal physiological needs without dehydration in preterm infants limits the risk of sequelae such as necrotizing enterocolitis (NEC) and a PDA [52].

Energy expenditure and fluid requirements may also significantly increase during stressful situations such as with surgery (up to 30% increase), severe sepsis (up to 50% increase), fever (10% per degree over 37 °C), and cardiac failure (up to 25% increase). These conditions may increase the need for augmented feeds, whether oral, gavage, or total parenteral nutrition (TPN).

Sodium is often omitted or severely reduced in the fluids administered to neonates in the first 24–72 h. Four factors modulate the fractional excretion of sodium: renin–angiotensin–aldosterone system, ANP, prostaglandins, and catecholamines [53]. It is in the distal tubule that these factors interact to maintain Na^+/K^+ concentrations and fluid balance. Judicious administration of sodium and fluids in the early postnatal period will prevent complications from hypo- or hypernatremia as well as fluid overload or dehydration. The serum sodium can be an accurate marker of the hydration status of the neonate with hyponatremia from fluid overload and hypernatremia resulting from dehydration.

Sodium and Electrolyte Requirements

Immediately after birth, both full-term and preterm infants are in negative sodium balance due to the physiologic natriuresis stimulated by ANP changes with birth [30]. The high fractional excretion of Na^+ (FE_{Na^+}) in term neonates (3.5%) decreases rapidly over the first 24 h postnatally, reaching adult levels (<1%) within the first few days [42]. In preterm neonates, the FE_{Na^+} is as high as 6–7% before 28 weeks gestation, decreasing slowly over the first postnatal month possibly to 2% [42, 54]. This can lead to negative Na^+ balance, hyponatremia, neurologic disturbances, and poor growth unless sodium is administered at a rate of 3–5 mmol/kg/day [40]. Preterm neonates demonstrate a greater negative sodium balance than term neonates, which may persist for many weeks after delivery because of decreased Na^+K^+ ATPase activity (i.e., limited resorption of sodium), increased ECF volume, and reduced tubular aldosterone sensitivity.

The diagnosis of hyponatremia in neonates remains controversial. Most recommend maintaining the serum sodium concentration between 135 and 145 mEq/L. Hyponatremia has been defined as a serum sodium concentration either <135 or <130 mEq/L [54]. In one study, the frequency of hyponatremia occurred in 4.3% neonates, using a definition in neonates of <130 mEq/L. Of those who were hyponatremic, 70% were preterm and 90% of the hyponatremia was due to iatrogenesis [55]. Hyponatremia was associated with a greater mortality, although the mortality was not due to the hyponatremia itself, but to the underlying cause. Extremely preterm infants who become hyponatremic most likely do not have reduced total body sodium, which would permit increasing their sodium intake. These infants require a reduction in total fluid intake. Conversely, the preterm infant is unable to rapidly respond to a sudden sodium load and initiate a natriuresis.

Clinically, important disturbances in acid–base status are unusual in full-term neonates unless protein intake is excessive. Factors that may contribute to metabolic acidosis in preterm neonates, who received TPN in the first postnatal week, include gestational age, initial base excess, and amino acid and lipid intake [56]. Plasma bicarbonate (HCO_3^-) concentrations depend on the renal HCO_3^- threshold, which is reduced in the full-term neonate (19–23 mEq/L) and even less in the preterm neonate (18–22 mEq/L), and very low birth weight (<1300 g) infants (14–18 mEq/L) [38, 40]. The reduced renal HCO_3^- threshold (physiological renal tubular acidosis—RTA) may be caused by the physiologic volume expansion in the preterm neonate and the relative immaturity of the tubular transport mechanisms [57]. Sodium bicarbonate or more commonly sodium or potassium acetate supplements of 1–2 mmol/kg/day are generally recommended for very small preterm infants depending on the defect identified. Infants with normal anion gap metabolic acidosis secondary to renal immaturity may have a greater requirement for alkali (acetate) in their parenteral nutrition.

Most tubulopathies that occur in neonates are associated with an unexplained metabolic acidosis. In terms of the acid–base balance, term and preterm neonates have a low threshold for spilling bicarbonate, although even preterm neonates can retain sufficient bicarbonate to manage an acid load. The

normal plasma bicarbonate is 20–22 mmol/L in term neonates and 18–20 mmol/L in preterm neonates. Tubular disorders that impact the acid–base status of a neonate can be traced to a defect in either bicarbonate resorption in the proximal and/or distal tubule or acid excretion in the distal tubule.

Tubular acidosis in neonates is usually inherited and involves either the proximal or distal tubules [57]. Proximal renal tubular acidosis (RTA type 2) is associated with a tendency to spill bicarbonate in the urine, presenting as a non-anion gap hyperchloremic metabolic acidosis [57]. The bicarbonate that is spilled in the proximal tubule is partially reabsorbed in the distal tubule in exchange for potassium, hence hypokalemia is common. RTA type 2 is treated with oral alkali, water resuscitation, and potassium. In contrast, distal renal tubular acidosis (RTA type 1) results from a defect in hydrogen ion excretion in the collecting ducts [57]. This results in a non-anion gap hyperchloremic acidosis, severe hypokalemia, and dehydration. In RTA type 1, the urine pH always exceeds 6.2. Distal renal tubular acidosis (RTA type 4) is the only RTA that is associated with hyperkalemia, which arises from a deficiency in aldosterone. The latter results in hyperkalemia, hyponatremia, and hypotension, with similar laboratory findings to RTA type 1 except for the hyperkalemia. If RTA persists uncorrected and untreated, chronic renal tubular acidosis or alkalosis can impair growth as well as calcium metabolism [57]. Early correction of RTA defects is imperative to prevent serious bone and growth defects.

Glucose

Insulin is first detected between 10 and 12 weeks of gestation, and it regulates organ growth such as skeletal and cardiac muscles, liver, and adipose tissue. The fetal effects of excessive insulin, such as that seen in fetuses of diabetic mothers, result in macrosomia. However, by 20 weeks, the fetal pancreas begins to respond to fluctuations in the glucose and amino acid concentrations by secreting insulin. However, insulin remains relatively inactive until the onset of corticosteroid activity in the second trimester, after which it begins to regulate the expression of enzymes related to glycogen storage and lipid synthesis. As a result, glycogen storage does not begin to accumulate (in the liver >> heart > skeletal muscle) until 27 weeks gestation and increases steadily thereafter until 36 weeks, after which it increases very quickly (at a rate of 50 mg/g of tissue) until term [58]. This reserve, less than 5% of the body weight, is rapidly depleted if a source of energy is suddenly needed (glucose-6-phosphatase is present only in the liver to release glycogen rapidly as an energy source for the neonate) [58], which is why a neonate, and a preterm neonate to a greater extent, is prone to hypoglycemia during prolonged fasts. In the term neonate, hepatic gluconeogenesis appears insidiously and only after birth; in the preterm and IUGR neonates, gluconeogenesis is severely impaired due to immature enzymes and insufficient precursors [58]. The placenta is permeable to triglycerides, free fatty acids, and glycerol, and insulin stimulates fatty acid synthesis in the liver and glucose uptake by adipose tissue, resulting in triglyceride synthesis. During the third trimester, fat is stored in adipose tissue, which comprises 16–18% of body weight at term. The accumulated fat amounts to an energy reserve of approximately 5000 kcal in the neonate.

Endocrine Response at Birth

Birth is associated with an endocrine stress response that is characterized by a massive increase in plasma catecholamine, glucagon, and cortisol concentrations and a decrease in insulin levels. The large ratio of glucagon to insulin induces hepatic glycogenolysis, lipolysis, and gluconeogenesis, effects that are also stimulated by increased concentrations of circulating catecholamines at birth. Nonetheless, blood glucose concentrations in neonates decrease physiologically immediately after birth, reaching a nadir by 1–2 h (concentration: 20–25 mg/dL) (1.1–1.4 mmol/L) and increase slowly thereafter, stabilizing by postnatal days 2–4 [58, 59]. The neuroendocrine responses during this transition period have been characterized as a hypoketotic, hypoglycemic response to incomplete suppression of insulin combined with increased glucagon and epinephrine release [60]. During this transition period, the brain ensures adequate energy sources by increasing cerebral blood flow and transport of glucose in addition to using other sources of energy.

The risk of all degrees of hypoglycemia in the term neonates is ~18% when neonates of diabetic mothers, small for gestational age, and late preterm infants are included [61]. Hypoglycemia occurred significantly more frequently in late preterm infants than in infants of diabetic mothers, large and small for gestational age neonates [61]. Of these preterm infants, 2.4% exhibited symptomatic hypoglycemia. Variability in the incidence of hypoglycemia can be attributed to different thresholds used to define hypoglycemia and the timing of the glucose concentrations related to birth and the last feed [61]. Factors that increase the risk of hypoglycemia in preterm neonates include prematurity, gestational age (the less the gestational age, the greater the risk (<33 weeks)), and maternal hypertension, whereas factors that decrease the risk include antenatal magnesium sulfate and labor [62]. In another study, prematurity, macrosomia, improper feeding, gestational diabetes mellitus, and hypothermia, but not gestational hypertension, were also associated with hypoglycemia [63]. Hepatic synthesis of glucose through glycogenolysis and gluconeogenesis is the only source of glucose until feed-

ing or parenteral nutrition is established. Estimates of glucose kinetics in full-term neonates suggest that healthy neonates produce glucose at the rate of 5–8 mg kg/min (or 28–45 μmol kg/min), of which 50–70% is contributed by gluconeogenesis. Liver glycogen stores (50–5 mg/g tissue) may be depleted within 12 h of birth, after which energy requirements are supported by oxidative fat metabolism until feeding is established. The rate of lipolysis, as estimated by the rate of appearance of glycerol or fatty acid, corresponds to 6–12 μmol kg/min.

Hypoglycemia

There is no consensus on the precise definition of either hypoglycemia or euglycemia in neonates [64], although most clinicians acknowledge that neonatal hypoglycemia can lead to seizures and poor neurocognitive outcomes. Most experts define hypoglycemia as a blood glucose concentration <47 mg/dL (<2.6 mmol/L) [62, 64, 65], although the basis for this threshold is curious at best [63]. According to AAP (American Academy of Pediatrics) guidelines, a glucose concentration between 25 and 40 mg/dL (1.39 and 2.2 mmol/L, respectively) during the first 4 postnatal hours is actionable. These levels warrant feeding, IV glucose, and rechecking the blood glucose concentration depending on the values [66]. Between 4 and 24 h postnatal, the threshold to intervene increases to <35 mg/dL (1.9 mmol/L) [66]. For another perspective, the World Health Organization defined hypoglycemia as a blood glucose concentration <45 mg/dL (2.5 mmol/L) [67]. The physiologically optimal range for the blood glucose concentration is 70–100 mg/dL (3.9–5.6 mmol/L), with a minimal optimal concentration of glucose, 60 mg/dL (3.3 mmol/L).

The definition of hypoglycemia in the neonate is based on a 1988 study of 661 preterm infants (<1850 g) in which the more days the blood glucose concentrations were <47 mg/dL (2.6 mmol/L), the worse the motor and cognitive development scores at 18 months of age [68]. In fact, the Bayley scores were 3.5-fold worse in those with neonatal hypoglycemia compared with those who had not. Radiologically, 66 neonates with hypoglycemia (<2.6 mmol/L) that lasted 3 to 34 days and symptomatology (seizures, irritability) had abnormal MRI findings with thinning of the white matter of the parietal/occipital lobes when compared to neonates without hypoglycemia [69]. Interestingly, the abnormal MRI findings did not correlate with the severity but did correlate with the duration of hypoglycemia. Close monitoring and evaluation of hypoglycemic neonates who were also hypoxic and/or asphyxiated during the perinatal period is imperative to evaluate for potential neurocognitive deficits. Two studies evaluated cognitive outcomes after neonatal hypoglycemia. In the first study, executive function in preterm infants <32 weeks, with hypoglycemia defined as <47 mg/dL (<2.6 mmol/L), was similar to those without hypoglycemic episodes, although surprisingly, those with a large variability in the glucose concentration, and consistently >54 mg/dL, experienced worse neurosensory impairment [70]. In a follow-up neurocognitive assessment for 15 years, the same authors found no difference in IQ between the two groups, although IQ is a very crude and imprecise metric of cognitive function [70]. In the second study, hypoglycemic neonates sustained worse executive and visual motor integration at 4.5 years of age than non-hypoglycemic neonates [71]. Children who had the most severe, recurring, and/or asymptomatic hypoglycemic episodes were the most impaired. No difference in neurosensory impairment was detected. Numerous explanations have been offered for these different findings [72, 73].

Hypoglycemia exists during two distinct periods: the first in the immediate 48 h postnatally and the second beyond the first 3 postnatal days. Transient hypoglycemia in the immediate postnatal period is usually self-limiting, may require a temporary infusion of glucose, and usually resolves spontaneously once feeds have commenced. The mechanism for the hypoglycemia postdelivery is thought to be a relative hypoketotic, hyperinsulinism state that is independent of whether the neonate is SGA or appropriate for gestational age [60]. There is a failure to adequately suppress insulin. In contrast, hypoglycemia beyond the first 2–3 postnatal days portends more serious glucose metabolic derangements involving glycogen stores and fatty acids, insulin secretion disturbances, and neuroendocrine disorders of cortisol and/or growth hormone [64, 72, 74]. Immature infants (e.g., ELBW or VLBW) or those who are ill (hypoxia, ischemia, or sepsis) may have higher glucose requirements and are more vulnerable to the consequences of hypoglycemia. Other infants at risk for postnatal hypoglycemia include infants of diabetic mothers, those who are large for gestational age (LGA > 90‰) or small for gestational age infants (SGA), infants with Beckwith-Wiedemann syndrome or intrauterine growth restriction (IUGR <10‰), post-asphyxiated infants (APGAR <5 at 5 min), and those with G6PD deficiency [64, 73, 75, 76]. An infusion rate of glucose of 3–5 mg/kg/min will prevent hypoglycemia in infants of diabetic mothers, a rate of 4–7 mg/kg/min will prevent hypoglycemia for most full-term neonates, and an infusion rate of 6–8 mg/kg/min will prevent hypoglycemia in ELBW and IUGR infants [74]. Serial monitoring of the blood glucose concentrations is advisable to avoid missing an episode of hypoglycemia that might lead to clinical sequelae such as seizures. In the operating room, the blood glucose concentration should be monitored as indicated, particularly if glucose is not administered to a neonate during surgery.

In the preterm neonates, the control of glucose is much more "brittle" with both hypo- and hyperglycemia occurring

to greater extremes and more frequently in these neonates. Hypoglycemia occurs because extreme prematurity limits the hepatic reserve of glycogen (glycogen accumulates primarily during the third trimester), and hyperglycemia occurs because exogenous glucose fails to suppress endogenous glucose production. In neonates <28 weeks gestational age, hypoglycemia is almost unavoidable in the first few hours after birth if exogenous glucose is not administrated. These infants have limited glycogen stores, decreased availability of amino acids for gluconeogenesis, and inadequate lipid stores for the release of fatty acids and fat stores to maintain glucose balance. Ketogenesis is severely limited in preterm neonates because they lack fat stores in adipose tissue (fat represents <2% of total body weight). Depending on its severity and the number of episodes or duration, hypoglycemia can produce devastating effects on the central nervous system (CNS) [77, 78]. Reduced blood concentrations of glucose invoke a stress response and alter cerebral blood flow and metabolism. During hypoglycemia, brain glucose metabolism decreases by up to 50%, relying primarily on alternate energy sources such as fatty acids and lactate. Preterm neonates appear less capable of offsetting these developments by providing alternative fuels and substrates for the brain than term neonates. Even moderate hypoglycemia can lead to an adverse neurodevelopmental outcome including an increased risk of motor and developmental delay, particularly in small for gestational age preterm neonates [78]. Cerebral injury is caused not only by severe and prolonged hypoglycemia but also by mild hypoglycemia and intermittent episodes when it is combined with mild hypoxia or ischemia. MRI detected white matter abnormalities in more than 90% of full-term neonates with symptomatic hypoglycemia (blood glucose level <45 mg/dL or 2.6 mmol/L) [30, 31]. MRI evidence of the CNS manifestations of hypoglycemia has been documented in the parietal and occipital lobes [69, 79, 80]. Factors that were associated with abnormalities on the MRI included the number of days of and prolonged/recurrent hypoglycemia, but not a lower blood glucose concentration than those with normal MRI findings. The minimum blood glucose concentrations, however, were less in those who developed seizures [69].

Hyperglycemia

Hyperglycemia (defined as blood glucose concentration greater than 125 mg/dL or 7 mmol/L or plasma glucose concentration greater than 150 mg/dL or 8.25 mmol/L) is commonly observed during the first week of life in preterm neonates <30 weeks gestational age [81]. In a study of 580 preterm infants, <27 weeks gestation age at birth, hyperglycemia occurred in 30% of the neonates was associated with a doubling of the 28-day mortality and a reduction in mortality with insulin [82]. Glucose infusions had only a modest impact on the persistent hyperglycemia, leading the authors to recommend closer monitoring of these preterm infants throughout their first postnatal month. Stress, corticosteroids, methylxanthine therapy, and administration of glucose at excessive rates could all induce neonatal hyperglycemia. Glucose is usually infused at rates between 4 and 7 mg kg/min to ensure basal glucose requirements in neonates. However, hyperglycemia may develop if glucose infusion rates exceed 8 mg/kg/min in neonates with birth weights >1 kg and if moderate infusion rates of 4–8 mg/kg/min were administered to VLBW neonates with birth weights <1 kg. Hyperglycemia, which usually occurs after an abrupt increase in plasma glucose concentration (e.g., after a bolus of 25% or 50% dextrose IV), has been associated with a greater risk of intraventricular hemorrhage. In the presence of ischemia or hypoxia, the impaired metabolism of excess glucose causes an accumulation of lactate and a decrease in intracellular pH that subsequently severely compromises cellular function that may result in cell death [77].

Enteral Nutrition (Trophic Feeding or Minimal Enteral Nutrition)

The nutritional requirements in preterm neonates during the first few days after birth are the greatest in the neonate's lifetime. During this period, the large nutritional demand is needed to double the preterm neonate's weight to ensure adequate postnatal growth. Other factors that may increase the metabolic requirements include chronic hypotension, acidosis, hypoxia, sepsis, and surgery. Feeding is less efficient in some late preterm compared with full-term neonates because the former fatigue quickly and have immature feeding skills (poor suck and swallow coordination). Additionally, these preterm neonates often have intestinal dysmotility, reduced intestinal enzyme activity, and may be receiving corticosteroids, all of which may lead to feeding intolerance with associated anesthetic implications. Finally, some infants require a longer-than-normal interval between feedings because of delayed gastrointestinal motility and gastric emptying [83]. Together, these may lead to the need for oral trophic gavage (tube) feeding until effective full oral feeding is possible [84]. The results of several Cochrane reviews and smaller studies on the effects of when to start first feeds, increasing feed rates, and the mortality and risk of developing NEC in VLBW neonates concluded that trophic feeds can begin before the 4th postnatal day, feed rates can be advanced to ≥24 mL/kg/day, and the risk associated with NEC is not increased [85].

Minimal or Small Volume Enteral Nutrition (Trophic Feeding)

Minimal enteral nutrition, minimal enteral feeds, or trophic feeding refers to the practice of introducing early enteral feeding with small volume feeds in preterm neonates. Several interchangeable terms for this type of feeding each hold a different implication: "trophic feeding" is based on the feed-stimulating intestinal growth, "priming feeding" refers to the feed-stimulating varied aspects of gut function, and "non-nutritive feeding" means that these feeds are not intended to provide either the sole or primary source of calories and nutrition for the neonate [86]. Starting volumes vary from 5 to 25 mL/kg/day with benefits noted at less than 1 mL/kg/day (priming). Minimal trophic feeds (either by bolus or continuous infusion of 10 mL/kg/day) in the first week of life stimulate the gut by increasing the activity of various enzymes, inducing mucosal growth, promoting motility, and preventing translocation of bacteria across the gut wall—a significant concern in VLBW infants [86]. Human breast milk (HBM) (colostrum) is preferred because it contains gastrin and prokinetic hormones; positive results have been reported with donor milk supplementing formula feeding in reducing NEC [86–88]. Feeding volumes are kept small, regardless of the size of gastric residuals, with volumes <20 mL/kg/day. Minimal enteral nutrition is often instituted in any scenario associated with gut hypoxia or decreased intestinal blood flow (asphyxia, hypoxemia, hypotension) and/or marked diastolic steal (e.g., a PDA).

Normal Enteral Feeds

Maturation of the gastrointestinal tract with increases in the intestinal length and surface area including villus and microvillus growth occur during the last trimester of pregnancy. HBM is the first choice for preterm and term neonates as it provides substantial benefits to the health of infants including reduced infections, inflammation, and enhanced neurocognitive development [89]. However, if unfortified, HBM may not provide adequate nutrients to meet the demands of preterm neonates, particularly in light of large variations in the protein and fat content of HBM. HBM from mothers of preterm neonates contains more protein than the milk from mothers of term neonates; initially, the HBM has a protein content of approximately 2.5–3 g/100 mL (colostrum), which decreases to approximately 1.5–2 g/100 mL soon after birth (transitional milk), and finally stabilizes at 0.9–1.4 g/100 mL (mature milk). In general, increased concentrations of protein persist for the first month of lactation. Thereafter, the protein content of preterm milk decreases and approaches the composition of full-term HBM. In contrast, preterm infants receiving 150 mL/kg/day of fortified HBM receive approximately 3.5 g/kg/day of protein.

Total Parenteral Nutrition

The smaller the infant, the greater the need for parenteral nutrition and the greater the urgency to initiate it to provide adequate nutrition for growth and development [90]. In the case of infants with birth weights <1500 g, total parenteral nutrition (TPN) starts on postnatal day 2 or 3 when the fluid and sodium balance has stabilized. Infants require 90–105 kcal/kg/day of TPN to achieve adequate growth; 40–50 kcal/kg/day is required just for the resting metabolic rate in a thermoneutral environment [90]. When supplementing orogastric feeds, the TPN may be increased to 150–160 mL/kg/day as tolerated to provide adequate calories for growth. The composition of TPN should be allocated according to the energy source: 30–35% of the energy from dextrose, 10–15% from proteins, and 25–40% from lipids [90]. Current practice in many NICUs is to initiate TPN with 2–3.5 g/kg/day of amino acids on the first postnatal day using "starter" or "vanilla" TPN solutions that are stocked in the NICU, increasing to 4 g/kg/day by the end of the first week. In both HBM and formulae, lipids contain the essential fatty acids, linolenic acid, and linoleic acid [90]. The primary reason for including parenteral lipids is to provide the essential fatty acids, which are important determinants of membrane lipid composition and central nervous system development. ELBW infants usually receive their dietary fat via parenteral lipid emulsions. There are concerns that lipid infusions in preterm neonates may confer adverse effects such as impaired oxygenation, increased risk of lung disease, impaired immune function, and increased free bilirubin levels. TPN may cause early and late adverse events including cholestatic liver disease for which there is some evidence that reduced lipid infusion rates and switching to fish-based fat sources have been salutary. Lastly, central-line infections have been serious complications in preterm infants whose TPN has been infused, necessitating anesthesia and anesthesia for line changes in some instances [90].

Fasting and Preoperative Oral Fluids

Fluid management in the neonate who is undergoing major surgery is complex, influenced by gestational age, postnatal age, physiological maturation of organ systems, type of surgery, concomitant illness, and blood loss. Furthermore, prematurity exacerbates these challenges as organ systems are immature and body fluid composition differs from that of a healthy, term neonate.

Careful fluid and electrolyte management is essential in the surgical neonate. Insufficient administration of fluids can cause hypovolemia, hyperosmolarity, metabolic acidosis, hypotension, and renal insufficiency, whereas excess fluid administration can cause generalized edema, congestive heart failure, and bronchopulmonary dysplasia (BPD). In the

VLBW infant, excess fluid administration may also be associated with a PDA because the fluid overload stimulates the production of PGE_2, which prevents the PDA from closing. In the infant with a large PDA, aortic blood is shunted into the pulmonary artery, reducing the proportion of blood flow to organs via the descending aorta. This then reduces intestinal blood flow, which may lead to hypoperfusion, and ischemia and raise the possibility NEC.

Readers are advised that much of the evidence regarding the management of fluids in neonates and small infants is derived from studies in the critically ill neonate; thus, caution must be exercised in extrapolating these data to the healthy neonate undergoing anesthesia and surgery.

Gastrointestinal Ontogeny

To understand gastric emptying and the risks thereof during anesthesia in neonates, a brief synopsis of the ontogeny of the upper gastrointestinal system is required.

By 20 weeks gestation, the fetal stomach has both the macro- and microscopic appearance of the stomach of the term neonate [90]. Gastric acid secretion is under the control of two mechanisms: endocrine (gastrin and histamine) acting directly on the parietal cells and/or via enterochromaffin-like cells and vagal stimulation [91].

Within the epithelium of the gastric rugae, four distinct cell types are present at birth, contributing to gastric secretions: parietal, chief, endocrine, and mucosal cells [92]. Each cell type contributes specific and essential constituents to gastric fluid. The parietal (oxyntic) cells secrete hydrochloric acid and intrinsic factor (for Vitamin B12 absorption). The chief (zymogen) cells secrete pepsin precursor, pepsinogen, that digests proteins. Endocrine cells secrete hormones that regulate acid secretion through histamine-releasing enterochromaffin-like cells and somatostatin-releasing D cells. These endocrine cells are present throughout the gastric epithelium except in the region of the pylorus, where gastrin (G) cells dominate. Lastly, mucous cells secrete mucous glycoproteins that protect the epithelium with a thick lining.

Parietal cells are capable of secreting hydrochloric acid by 19 weeks gestation, and of maintaining gastric fluid pH <2 at 24 weeks gestation [91]. The density of parietal cells is two- to three-fold greater in the epithelium of the neonate than the adult, although the antrum may lack parietal cells in the majority of term neonates [92]. Intrinsic factor production begins during the first couple of postnatal days, reaching 80% of adult values by 2 months postnatal age. The parietal cells in the neonate appear relatively insensitive to gastric stimulation [93]. Chief cells are present in fewer numbers in the neonate compared with the adult and secrete only 1/15th as much pepsin on the day 1 as does adult epithelium [92]. Thereafter, the pepsin production increases steadily and quickly, reaching one-half the adult output by 5 months and the full adult output by 2 years of age [92]. G cells, which produce gastrin, are present in the pylorus in the fetus between 12 and 18 weeks gestation [91]. Gastrin is both a potent trigger for gastric acid release and a trophic hormone. In neonates, the circulating gastrin concentration exceeds maternal levels for the first 4 months, although the surge in gastrin levels within 30 min of feeding (HBM or formula) during the first 2 postnatal months is less than that in adults and without an increase in gastric acid secretion [94].

Gastric Fluid pH and Volume

Gastric fluid pH reaches 6–7 within minutes after birth in term neonates, decreasing to 5.4 within the first hour, to 3.1 by 1–2 h, and then leveling off at a pH of 2.2 after 5–6 h where it remains into adulthood [95, 96]. The alkalinity of the gastric fluid immediately after birth has been attributed to amniotic fluid that was swallowed during parturition (amniotic fluid buffers the gastric juice) or reduced gastric acid secretion as a result of reduced gastrin secretion in the postnatal period [92]. Gastric fluid pH in term neonates is less after vaginal delivery and any labor state compared with elective C-sections, and is most acidic after a precipitous labor, possibly due to less amniotic fluid swallowed during a stressful delivery. Within 2 h of birth, gastric acid secretion commences via gastrin, although acid production remains meager for a while, increasing during the subsequent 4 months by 400% as the pH decreases dramatically [92].

The gastric fluid pH on the first postnatal day becomes even more alkaline (>7) in preterm neonates <34 weeks gestation than in term neonates. However, preterm infants as young as 24 weeks gestation are capable of acidifying the gastric fluid to a pH <4 after the first postnatal day. The gastric fluid pH in preterm infants 24–29 weeks gestation ranges from 1.8 to 3.7 after the first postnatal day (the gastric fluid pH was <4 in 100% of infants) and decreases to 1.7–2.0 by day 16 [91]. Gastric acid output reaches adult values between 6 months and 2 years [92, 97]. The greater gastric pH in preterm neonates is independent of the nature of the delivery and may be explained by the lack of exposure to the surge in cortisol that occurs after 34 weeks gestation. Acidification of the gastric fluid offers protection to the gut mucosa from microorganisms, although it predisposes to mucosal erosion and the risk of ulceration and perforation. An off-setting effect is offered by prostaglandins, which in combination with epidermal growth factor increase bicarbonate secretion, reduce acid secretion, and render the epithelium more hydrophobic. HBM increases the gastric fluid pH >4 for 90 min, with q3h feeds offering protection against gastric epithelial damage and perforation [91]. Exogenous dexamethasone and indomethacin inhibit prostaglandin production and morphine increases histamine release, each increases the risk of

gastric mucosal damage [91]. Although rare, gastric perforation in the preterm infant is devastating, carrying a 50% mortality.

Swallowing is first detected in the fetus at 12–16 weeks gestation. At that time, the fetus swallows 2–7 mL/day but the volume increases rapidly to 300–700 mL/day as term gestation approaches [92]. Fetal studies have tracked swallowing beginning at 24–26 weeks gestation and identified a cyclical filling and emptying of amniotic fluid every 45 min. Between 14 and 24 weeks gestation, irregular gastric peristalsis occurs while the difference between the maximum and minimum gastric area is 3%. After 24 weeks, gastric peristalsis becomes regular and the difference in the gastric area increases gradually such that by 32 weeks gestation the difference is 8%, signifying gastric volumes sufficient to permit feeds [98]. Gastric fluid volume in the unfed neonate ranges from 0 to 10 mL [98, 99].

Gastric Emptying

The notion that all patients should fast before surgery holds very different implications for neonates compared with older infants and children. In part, because 50% or more of neonatal surgeries are urgent or emergent (bowel atresia, malrotation, or NEC), the neonates are often less than 48 h old and, in many instances, have never been fed. IV dextrose solution may be their only source of nutrition at the time of surgery. For the remainder, the neonates are scheduled for elective surgery, are older than 48 h, and have likely consumed HBM or formula as their last and only feeds in this first postnatal month. Accordingly, we restricted the discussion of fasting in neonates clear fluids, HBM, and infant formula.

The gastric emptying time after clear fluids in neonates is one-third that after HBM and one-fifth that after formula [100]. Gastric emptying times after clear fluids are slower with an increased osmolality such as a greater dextrose concentration. To date, evidence in children suggests that a fasting interval of ~1 h after clear fluids had no effect on the risk or frequency of aspiration, although none of the studies published to date actually achieved a clear fluid fasting interval of <1 h. Moreover, a very tight relationship exists between the fasting interval after clear fluids and residual gastric fluid volume after clear fluids [101], that is, as the fasting interval decreases, the residual gastric fluid volume increases exponentially. Nonetheless, gastric fluid volume alone does not increase the risk of aspiration pneumonitis and evidence to date indicates that clear fluid aspiration is usually well-tolerated. Gastric emptying studies after clear fluids in neonates have not been forthcoming.

Although several techniques have been used to measure gastric emptying after HBM and formula feeds in the past, here we consider all of the techniques to have equipoise. Most of the evidence published to date indicates that feeds including fluids empty from the stomach exponentially, that is, the larger the volume the more rapid the elimination. Neonates feed every 2–4 h, and about 80% of neonates are fed HBM (not necessarily exclusively) in the United States [102]. In term and preterm neonates, the gastric emptying half-time after HBM is less than that after formula (Fig 8.4 and Table 8.3) [88, 103, 104]. The gastric emptying half-times in term and preterm neonates are: for water, ~15 min; for HBM, ~48 min; and for formula, ~78 min. Thus, the estimated 98% gastric emptying times for these three feeds are 4× half-lives or 1 h, >3 h, and >5 h, respectively, which correspond to the fasting times adopted by most societies of anesthesiology globally: 2 h for clear fluids, 4 h for HBM, and 6 h for formula (Table 8.4) [109–111]. *Note*: The APAGBI failed to reach consensus regarding the duration of preoperative fasting after HBM and formula [109] and the SSAI preoperative

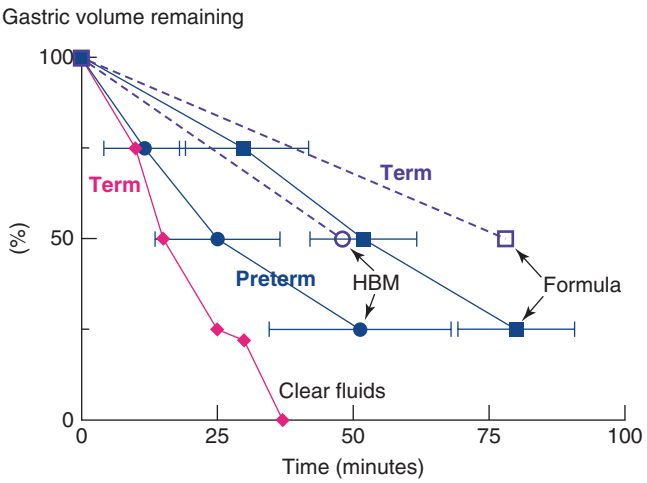

Fig. 8.4 Gastric emptying times for water, human breastmilk (HBM), and infant formula. The half-time for emptying water in neonates and young infants is 15 min, for HBM is 48 min, and for formula is 78 min. Data are adapted from Refs. [100, 103, 104]

Table 8.3 Gastric emptying half-time (minutes)

	Term neonate	Preterm neonate				
Water	15m [100]					
HBM	48 ± 15 [104]	25.1 ± 11.5 [103]	36 [87]	47 [88]	61 [105]	35 [106]
Formula	78 ± 14 [104]	51.9 ± 9.8 [103]	72 [87]	65 [88]	76 [105]	45 [106]
	64 ± 7.1 [99]	34 ± 4.9 [99]				
Casein vs whey-based formula		56.5 ± 15 vs 65 ± 12.3 [107]				

HBM Human breastmilk

Table 8.4 Fasting guidelines

Reporting body	Year	Duration of preoperative fasting (h)			Additional recommendations for neonates	Reference
		Clear fluids	HBM	Solids		
Taskforce on Scandinavian preoperative fasting guidelines	2005	2	4	6	Minimum 3 h fast breast milk	[108]
APAGBI	2007	1	3 (<6 months) 4 (<6 months)	Formula 4 (<6 months) 6 (>6 months)		[109]
ESPA	2011	2	4	6	Healthy neonates Clear fluids 2 h; HBM 4 h; Cow's milk 6 h	[110]
ASA Guidelines	2017	2	4	6	Healthy neonates <44 weeks PMA; HBM 4 h; Infant formula 6 h; Non-human milk 6 h	[111]
Swedish Guidelines	2018	0	4	6	Actively encourage HBM or formula 4 h preop	[112]
APAGBI, ESPA, ADARPEF	2018	1	3	6	No specific recommendation	[113]

Fasting guidelines recommended by the Association of Paediatric Anaesthetists of Great Britain and Ireland (APAGBI), the European Society for Paediatric Anaesthesiology (ESPA), and L'Association Des Anesthésistes-Réanimateurs Pédiatriques d'Expression Française (ADARPEF)

HBM Human breastmilk

Solids include all non-human milk, formula milk, and any other solid food

fasting guidelines recommended age-specific guidelines for infants: a 4 h fasting interval for both HBM and infant formula for infants <6 months of age [108, 114].

During the first 3 postnatal months, 35–45% of those neonates who were breastfed received supplementation with infant formula [102], which complicates fasting guidelines as formula is emptied from the stomach more slowly than HBM. Several factors slow the rate of gastric emptying of feeds: feeds that contain long-chain versus medium-chain triglycerides, feeding with the neonate supine or in the left lateral decubitus position, with brief intervals between feeds and with smaller feed volumes, and the presence of concomitant diseases (such as acute respiratory distress) [83, 100, 115–119]. Other factors have minimal or conflicting effects on gastric emptying of feeds. These include the volume of HBM, temperature, casein/whey ratio, and osmolality of the feed, age of the preterm infant, phototherapy, and non-nutritive sucking [83, 107, 115, 117, 120, 121].

Conservative recommendations for the fasting after human and animal milk feeds (Table 8.3) are based, in part, on the mean gastric emptying times, the large interindividual variances in gastric emptying for both HBM and formula, the exponential nonlinear gastric emptying curves, and the fact that many mothers mix the two feeds (Fig. 8.4) [87, 104]. Given the very low risk of regurgitation and aspiration pneumonitis should regurgitation occur, some have suggested that the fasting interval after milk products could be reduced, based on preliminary data on gastric emptying [122]. A model-based meta-analysis of gastric emptying studies also indicated only marginally smaller mean gastric residence times after HBM compared with infant formula, although they too demonstrated enormous variances in the emptying times [121]. Before considering abbreviating gastric emptying times after milk-based feeds, it is important to appreciate that the pulmonary effects of milk products are much more injurious than clear fluids. In infant rabbit and mice models, instillation of HBM and infant formula produced substantive lung injury, with physiological, cytokine, and histological infiltrates in contrast to the lack of effect by clear fluid aspiration [123–125]. Before reducing the fasting intervals after milk products in neonates, it is crucial to bear this evidence and ensure that any perceived benefits are not outweighed by the well-known risks.

The Ideal Intraoperative Maintenance Fluid

In 1957, Holliday and Segar proposed the 4–2–1 mL/kg/h formula to determine the rate of administration of maintenance fluid for healthy hospitalized neonates, infants, and children based on calorific requirements, insensible and urinary losses, and an allowance for the water of oxidation produced during metabolism [126]. They proposed that IV fluid therapy should be hypotonic instead of isotonic fluid and at rates based on body weight rather as the neonate is unable to excrete excess water and excess sodium. They estimated that pediatric electrolyte requirement was a midpoint between that received by consumption of HBM and that recommended in adults and suggested that children need 2–4 mmol/kg/day of sodium and 1 mmol/kg/day of potassium. Their supposed ideal solution for maintenance contained 30 mmol of sodium (4% dextrose and 0.18% saline or 4% and 0.2% saline) and is hypotonic [127]. This was the standard pediatric intravenous solution until the late 1980s at which time a cluster of children developed hyponatremia, seizures, aspiration, and brain damage upon emergence from anesthesia after receiving large volumes of hypotonic solutions during surgery [128]. It was at this time that a paradigm shift in practice occurred to replace hyponatremic, glucose-containing maintenance fluids for all children admitted to the hospital, as well as those undergoing anesthesia and surgery with isotonic solutions [129–131]. Opinion differs on whether any glucose is required in children >1 year of age to replace third space losses as hypoglycemia and ketosis are exceedingly rare. In some countries, balanced salt solutions with 1–2% glucose have been developed for pediatric use in the perioperative period [132]. We confine our discussion to the neonate, in which balanced salt solutions are used to replace estimated extracellular fluid losses and hypotonic glucose/calcium solutions from the NICU are continued as maintenance solutions in the operating room (Fig. 8.5). For elective surgery in neonates where IV access has not yet been established and glucose is not infusing, isotonic or near-isotonic solutions with small concentrations of glucose (~2%) seem appropriate along with serial serum glucose testing [133].

Hyponatremia

Hyponatremia, defined as a serum sodium <135 mmol/L, occurs in 9–24% of hospitalized children receiving hypotonic intravenous solutions [130, 134–136]. Hyponatremia (<115 mmol/L) is primarily caused by extrarenal loss of electrolytes, in the presence of increased ADH activity and the administration of hypotonic fluids [129]. Morbidity and mortality associated with acute severe hyponatremia (Na <130 mmol/L) results from acute cerebral edema, and may include headache, lethargy, and seizures, and potentially even respiratory and cardiac arrest secondary to brain stem herniation. Because of their greater brain/intracranial volume ratio, infants are at increased risk for these sequelae compared with adults. The original 4–2–1 IV fluid maintenance recommendation was never intended for use in the

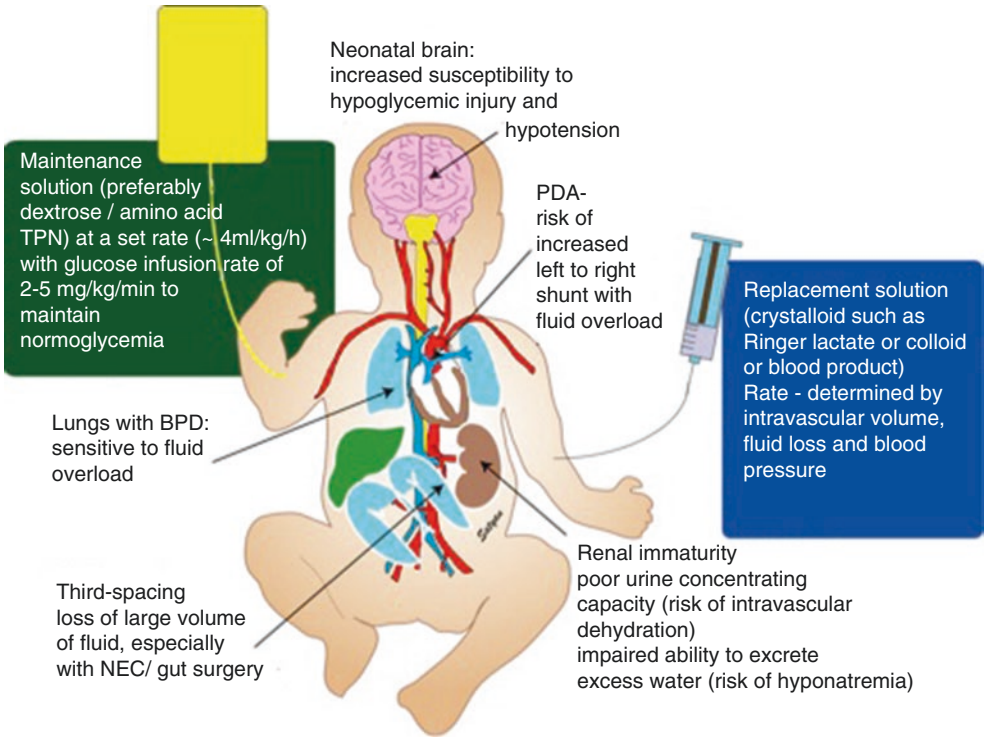

Fig. 8.5 Principles of intraoperative fluid management. Fluid therapy in the operating room consists of two components—maintenance and replacement fluids. The maintenance fluid consists of a dextrose-containing solution (preferably the same preoperative TPN solution) to maintain normoglycemia. The maintenance fluid should be infused at the same rate as preoperatively. The replacement solution should be a balanced salt solution such as Ringer's lactate solution or a colloid (albumin) or blood product and is administered to maintain adequate intravascular volume and pressure and to replace any deficit or ongoing losses. Premature infants with bronchopulmonary dysplasia (BPD) and/or a PDA are susceptible to fluid overload. The brain of the neonate is particularly vulnerable to hypoglycemic injury. Cerebral circulation is pressure-passive with limited autoregulation and susceptible to hypotension. Abdominal surgery (especially NEC) is associated with increased "third-space" losses into the gut requiring increased replacement fluid therapy. The immature kidney is unable to handle the increased water load, thereby increasing the risk of hyponatremia. See text for details

operating room because the perioperative period is commonly associated with markedly upregulated ADH levels and water retention [137]. Judicious restoration of euvolemia (after 10 mL/kg isotonic solution boluses over 20 min and repeated as needed) in infants and children (without cardiac and renal dysfunction) in the perioperative period downregulates ADH (Table 8.1) and reduces the risk of developing perioperative hyponatremia [35]. If ADH release is not quelled by reestablishing euvolemia, a surge in ADH will occur despite effective regional anesthesia or opioid dosing to preclude a stress response as evidenced by normal blood cortisol, insulin, and glucose concentrations [138]. The fluid status in the neonate should be assessed serially using hemodynamic metrics to gauge when to cease or reduce the balanced salt to preclude a fluid and sodium overload, for which the neonate is ill-equipped to manage and which may increase morbidity. By downregulating the ADH levels, the risk of developing hyponatremia from the water load from the hypotonic maintenance solution and the isotonic balanced salt solution is diminished.

In 2007, the National Patient Safety Agency (NPSA) in the United Kingdom recommended that 0.18% saline 4% glucose be removed completely from general pediatric wards and replaced with 0.9% or 0.45% saline [139, 140]. When treating conditions considered to be at high risk of hyponatremia (including serum sodium level in the lower normal reference range, intravascular volume depletion, and other conditions), the alert advised the use of isotonic solutions (e.g., 0.9% saline with or without glucose).

Intravenous Solutions

A large number of isotonic intravenous solutions are now available for pediatric intravenous infusion (Table 8.5). Although some of these fluids are available in Europe, elsewhere glucose-containing isotonic fluids are not commercially available in the operating room. Thus, for neonates who arrive from home or who are not receiving 10% dextrose infusions from the NICU, we prepare 1 or 2% dextrose

Table 8.5 Characteristics of common crystalloids compared with human plasma

	Sodium (mmol/l)	Potassium (mmol/l)	Magnesium (mmol/l)	Calcium (mmol/l)	Chloride (mmol/l)	Lactate, gluconate, malate	Osmolality (mOsm/l)	Osmolarity (mOsm/l)	pH
Plasma	136–145	3.5–5.0	0.8–1.0	2.2–2.6	98–106		291	287	7.35–7.45
0.9% sodium chloride	154	0	0	0	154		308	286	4.5–7.0
4% dextrose with 0.18% saline	31	0	0	0	31	0	284		4.5
Ringers Lactate	130	4	0	3	109	28	278	256	5–7
Hartmann's Lactate	129	5	0	2	109	29	254	278	5–7
Plasma-Lyte 148	140	5	1.5	0	98–106	27/23	295	271	7.4*
Sterofundin	145	4	1	2.5	127	24	309	Not stated	5.1–5.9
Ionosteril ISO	137	4	1.25	1.65	110	36.8	291	270	6.9–7.9
10% dextrose	0	0	0	0	0	0		278	3.5–5.5
4% albumin	130–160	0	0	0	130.160		310	250	7

*Plasmalyte osmolarity varies depending on country of manufacture. Plasmalyte pH varies from 6.5 to 8.0 depending on country of manufacture. Ionosteril manufactured by Fresenius Medical Care, Schweinfurt, Germany. Sterofundin manufactured by BBraun Melsungen, Germany. Osmolality measures the number of osmoles in a weight (kg) of solvent. Osmolarity measures the number of osmoles in a volume (L) of solvent

solutions in the isotonic clear fluid in the operating room in 100 mL buretrols by adding 2 or 4 mL of D50W in 98 or 96 mL of the isotonic solution, respectively. One hundred milliliter is usually sufficient maintenance fluid volume for most surgeries in neonates.

Glucose-Containing Solutions

Feeding the neonate after birth is essential for proper growth and development. Who to feed with what feed, by which route, how frequently, and when are questions that beg answers [141, 142]. For the neonates, the answers are simple. After the glucose concentration stabilizes in the postnatal period, oral feeds are often initiated, unless the neonate is diagnosed with a congenital anomaly that precludes feeding. In the latter case, TPN may be needed to provide nutrition either temporarily or for an extended period. In the case of preterm neonates, immaturity of the sucking reflex requires the use of orogastric tube feeds in the interim provided that may be supplemented with TPN if insufficient nutrition can be delivered. These factors must be evaluated based on the gestational age of the preterm infant and concomitant diseases. Nonetheless, some meta-analyses suggest that early gastric feeding is possible in select preterm infants and when the frequency and volume of the feeds are carefully titrated [85]. As the sucking reflex and gastrointestinal system mature, TPN can be phased out, the gastric tube removed, and oral feeds instituted. Evidence from a systematic review favors HBM in VLBW to reduce the risk of morbidity in this population of preterm infants [143].

Neonates require 4–8 mg/kg/min (approximately 300 mg/kg/h) of glucose to sustain brain development and preclude adverse neurocognitive outcomes [144]. The risk of hypoglycemia in neonates increases with prematurity, perinatal stress or asphyxia, small for gestational age infants, maternal diabetes, and Beckwith-Wiedemann syndrome (see above the "Hypoglycemia" section). Neonates who are treated with TPN or glucose infusions are also at risk for hypoglycemia if the infusion is stopped before or during anesthesia or the infusion rate is dramatically decreased. How much glucose neonates require during the perioperative period remains unclear. Neonates are capable of mounting a substantive neuroendocrine response to both surgical stress and in the case of preterm infants, reduced glycogen supply. This manifests as an increase in plasma cortisol, glucagon, catecholamines, and vasopressin, along with a decrease in circulating insulin. The result is an increase in the blood glucose concentration through gluconeogenesis, fat mobilization, and protein catabolism. In VLBW neonates who are ventilated for prolonged periods or septic, stress may trigger as a hyperglycemic response even before surgery commences, e.g., in a perforated bowel [145]. However, such compensation occurs at the expense of valuable energy reserves, namely, glycogen, fat, and proteins. In the case of preterm neonates, there is a limited supply of glycogen, which increases the risk of hypoglycemia in this age group. Furthermore, if a stress-free anesthetic is administered or the neonate is severely preterm, then the above neuroendocrine response may fall short of mobilizing sufficient glucose to maintain euglycemia [138]. In a survey of pediatric anesthesiologists, 76% administer glucose-containing solutions to neonates and 58% monitor the glucose perioperatively [146]. Accordingly, we recom-

mend maintaining the IV glucose solution (including TPN) rate during surgery; decreasing the infusion rate may result in a disproportionately increased insulin level that could cause hypoglycemia. If the infusion rate of glucose is adjusted during surgery, then "at-the-bedside" plasma concentrations of glucose should be measured periodically as clinically indicated.

The results of two studies of the effects of continuing a 10% dextrose solution at standard maintenance rates or switching to Lactated Ringer's solution during surgery in neonates demonstrated that the plasma glucose concentrations increased at the end of surgery in both studies, although the glucose concentration doubled in the neonates who received the glucose infusion but increased only modestly in the Lactated Ringer's solution at the end of surgery [147, 148]. Of greatest importance perhaps was the frequency of hypoglycemia in the Lactated Ringer's solution group, threefold greater than in neonates who continued the glucose infusion. Furthermore, the increased blood glucose concentration remained significantly greater than baseline for up to 8 h postoperatively. The authors attributed the increase in the plasma glucose concentration to the metabolic and endocrine responses to surgical stress, to an increase in counterregulatory hormones, primarily epinephrine, and glucagon and recommended perioperative glucose monitoring to prevent large swings in plasma glucose concentrations. In 2007, the Association of Paediatric Anaesthetists of Great Britain and Ireland issued consensus guidelines for maintenance fluids in term neonates [109]. They recommended 10% dextrose at 2–3 mL/kg/h in the first 48 h after birth, followed by 10% dextrose in N/5 saline at 4 mL/kg/h from the 3rd day onwards. Children of low birth weight, prolonged surgery (more than 3 h), or where the stress response is attenuated by regional anesthesia should have serial monitoring of blood glucose or should receive a 1–2.5% dextrose-containing maintenance fluid.

Few studies have investigated the glucose, lipid metabolism, and hormone responses in neonates during anesthesia and surgery [132, 149, 150]. The studies were conducted on neonates and infants, with the exception of neonates who required preoperative dextrose infusions, were preterm, or were infants of diabetic mothers. Dextrose solutions between 1 and 4% were studied and the resultant metabolic responses to the infusions were compared postoperatively. Surprisingly, the blood glucose concentrations 24 h postsurgery, as well as the incidence of hyperglycemia and the glucagon/insulin ratio after 1% dextrose, were greater than those after 4% dextrose. Combined with the metabolic responses, the studies supported a 2–4% dextrose infusion in the perioperative period in neonates. We believe that the data support 2% dextrose infusions for neonates in the perioperative period to prevent hypo- and hyperglycemia and to ensure stable metabolic indices.

Perioperative Fluid Management

General Principles

Current fasting guidelines recommend clear fluids 0–2 h preoperatively, HBM 4 h, and infant formula 4–6 h, limiting the duration of the fasting period (Table 8.4) [109–111]. Infants who meet these criteria usually have only minor fluid deficits that are generally not necessary to correct. However, if a neonate is suspected of being dehydrated due to a prolonged fast on the ward or if he/she is coming to surgery from the NICU, NICE guidelines recommend that the neonate should be given 10–20 mL/kg of an isotonic (sodium concentration 135–145 mEq/L) glucose-free solution over 10 min and then reassess for their volume status before considering a second fluid challenge [109]. We routinely administer 10 mL/kg IV of Lactated Ringer's solution before inducing anesthesia in neonates from the NICU and repeat the dose if blood pressure wanes ≥25% systolic from baseline.

Continuing TPN with amino acids (but without lipids) before and during surgery is a common practice and has the theoretical advantage of providing optimal nutrition while avoiding reactive hypoglycemia during catabolism associated with surgery. We routinely discontinue intralipid as the presence of lipid is a source of contamination if the intravenous line is used to administer medications or other fluids during surgery. If the intralipids are delivered through a separate line, then lipids may be continued during surgery. Three practical issues regarding the use of parenteral nutrition are the following:

1. *Partial parenteral nutrition with feeds*: Many infants undergoing semielective or elective surgery are receiving partial feeds and partial parenteral nutrition supplementation. The composition of partial parenteral nutrition fluids may include a large concentration of electrolytes (such as sodium, calcium, and potassium) and dextrose to compensate for low mineral content of oral feeds (specifically HBM). When the infant's oral feeds are stopped for preoperative fasting, the partial TPN should not be increased to full volume. Instead, a new TPN solution with optimal glucose and electrolytes at full volume (often 100–150 mL/kg/day) should be initiated. Alternately, the neonate's feeds may be supplemented with a plain crystalloid solution such as 5% dextrose in water (through a Y connector) to provide a partial TPN solution.
2. Parenteral nutrition is usually administered through a thin percutaneous or peripherally intravascular central catheter (PICC line). These catheters have a small internal diameter (usually 1.9-Fr lines) and offer large resistance. They are not suitable for emergency fluid boluses and are at a large risk of rupturing if small syringes (1–3 mL size)

are used to inject fluid volumes rapidly because of the great pressures that can build up within the catheter.

3. *Y-site compatibility of medications with parenteral nutrition solution*: In 2007, Roche laboratories updated their prescribing information for ceftriaxone sodium to include a contraindication for the coadministration with calcium-containing intravenous solutions in neonates due to reported fatal cases of pulmonary and renal precipitates (Rocephin package insert). Readers are referred to a detailed review of which medications are compatible with lipid- and non-lipid-containing parenteral fluids [151]. Table 8.6 highlights the compatibility of some commonly used medications with 2-in-1 (amino acids + glucose/electrolyte solution) and 3-in-1 (amino acids + lipids + glucose/electrolyte solution) parenteral nutrition solutions.

Perioperative Steroids

Preterm infants are occasionally treated with courses of corticosteroids such as hydrocortisone or dexamethasone to facilitate extubation, manage lung disease, or treat resistant hypotension. Some of these infants may develop adrenocortical insufficiency with a suppressed HPA axis if more than an occasional pulse dose of steroids has been administered. Adrenocortical insufficiency has been associated with circulatory collapse in the perioperative period, although it is likely that these infants and children were hypovolemic and that likely caused or exacerbated the circulatory instability. Most of the reports predated current practices of fluid loading neonates and infants before induction of anesthesia. With the difficulty in evaluating whether the HPA axis is intact, a stress dose of hydrocortisone is currently recommended before surgery for these infants to attenuate the risk in hypotension.

Emergency Surgery

For surgery that is emergent, neonates should be immediately resuscitated with fluids. Abdominal emergencies (volvulus or pneumoperitoneum after NEC) are associated with extravasation of fluid from the vascular space into the lumen. Restoration of intravascular volume using crystalloids (isotonic saline or Ringer Lactate), colloids (albumin) or blood products (platelets, packed RBCs, or fresh frozen plasma) is important. Conditions associated with vomiting or aspiration of gastric contents (such as pyloric stenosis, duodenal atresia, or stenosis) are associated with abnormalities in serum sodium, potassium, bicarbonate, and chloride. Infants with pyloric stenosis present with hypokalemic alkalosis and require resuscitation with fluids that contain adequate amounts of both chloride and potassium before they are scheduled for surgery.

Maintenance Fluids

Intraoperative fluid therapy can be optimally achieved with two different types of fluids administered at different rates: a dextrose-containing solution (preferably TPN) for maintenance fluids at a set rate (usually 100 mL/kg/day or 4 mL/kg/h) and a separate solution to replace liquids (crystalloids such as Ringer Lactate or colloids or blood products) (Fig. 8.5 and Table 8.7). The APA consensus guideline on perioperative fluid management in children did not reach agreement on what type and volume of fluid to give a term neonate after day 3 of life, but most neonatologists would recommend that the maintenance fluid should be 10% dextrose with Na (3 mmol/kg/day) and K (2 mmol/kg/day) given at a rate of 4 mL/kg/h or 100–120 mL/kg/day [109].

The Myth of the Third Space

Third space refers to the sequestration of fluid to a nonfunctional extracellular space that is beyond osmotic equilibrium with the vascular space [155]. During surgery, insensible fluid losses (third space losses) vary widely depending on ambient conditions. Preterm or low birth weight infants have a greater surface area-to-weight ratio, lose more water by evaporation, and consequently require more replacement fluid. Fluid losses from the respiratory tract may be rather significant in small infants and influenced by the degree of humidification of the inspired gases.

Traditionally, "Third space" losses were replaced with crystalloid solutions at rates from 1 mL/kg/h for minor surgery to 10 mL/kg/h for large open surgeries in term neonates to 50 mL/kg/h during surgery for NEC in preterm infants. Third space losses are less when procedures are performed laparoscopically.

More recently, the concept of the third space and fluid sequestration therein have been questioned. As a result, more restrictive fluid protocols were adopted in adults and associated with better outcomes. A Cochrane analysis of restricted versus liberal water intake for reducing morbidity and mortality in preterm infants reported that cautious restricted water intake while avoiding dehydration reduces the risk of PDA, BPD, NEC, and death [52].

Replacement of Intraoperative Losses

There is currently no consensus on using isotonic solutions as perioperative maintenance fluids in neonates, in part

Table 8.6 Y-site compatibility of medications with parenteral nutrition solution

Medication	2-in-1 TPN	3-in-1 TPN	Comments
Acyclovir	I	I	White precipitate forms immediately
Albumin	C	I	
Alprostadil	C	–	
Amikacin sulphate	C	Conflicting data	
Amphotericin B	I	I	Yellow precipitate formation
Ampicillin	Conflicting but administered in some units		
Atracurium	C	–	
Bumetanide	C	C	
Buprenorphine	C	C	
Caffeine citrate	C	–	
Cefazolin	Incompatible if dextrose concentration is 25%	C	
Cefotaxime	C	C	
Cefepime	C	–	
Cefoxitin	C	C	
Ceftazidime	C	C	
Ceftriaxone	I	I	
Dexamethasone	C	C	
Diazepam	C	–	
Diphenhydramine	C	C	
Dobutamine	C	C	
Dopamine	C	Conflicting	
Epinephrine	C	–	
Famotidine	C	C	
Fentanyl	C	C	
Furosemide	?		Small amount of precipitate forms in 4 h in select formulations
Heparin	C	I	
Hydrocortisone	C	C	
Insulin	C	C	
Isoproterenol	C	C	
Lorazepam	C	I	
Meperidine	C	C	
Methylprednisolone	C	C	
Metronidazole	C	C	
Midazolam	I	I	White precipitate forms immediately in select formulations
Milrinone	C	–	
Morphine	C	?	
Norepinephrine	C	C	
Ondansetron	C	I	
Oxacillin	C	C	
Penicillin G potassium	C	C	
Pentobarbital	C	I	
Phenobarbital	C	I	
Phenytoin	I	I	
Propofol	C	–	
Ranitidine	C	C	
Sodium bicarbonate	I		Small amount of precipitate forms in 1 h in select formulations
Vancomycin	C	C	
Vecuronium	C	–	

C compatible, *I* incompatible, – data not available, ? data not available, 2-in-1 (amino acids + glucose/electrolyte solution), and 3-in-1 (amino acids + lipids + glucose/electrolyte solution)

Table 8.7 Consensus statements on fluids

	Year	Fluid deficit	Maintenance term neonates postnatal <48 h	Maintenance term neonates postnatal >72 h	Intraoperative fluids	Isotonic fluids	Postoperative fluids	Reference
APAGBI	2007	Third space losses 1–2 mL/kg/h peripheral surgery 4–7 mL/kg/h thoracic surgery	10% dextrose 2–3 mL/kg/h or 40–80 mL/kg/day	10% dextrose 0.18% saline First 48 h of life 2–3 mL/kg/h	Term and preterm infants: no glucose solution unless already receiving glucose to continue	0.9% saline or Ringer's lactate solution		[109]
European Consensus Statement	2011				Isotonic with 1–2.5% glucose			[152]
Belgian Association for Paediatric Anaesthesiology	2012	Hourly maintenance multiplied by hours fasting and replace 50% first hour and 25% 2nd and 3rd hour		0.9% saline 5% dextrose or 0.2% saline 5% dextrose	Isotonic with 1% glucose full maintenance volume	Plasmalyte, Hartmann's solution, 0.9% saline	Minor surgery: isotonic with 1% glucose Major surgery: isotonic with 5% glucose 70% maintenance volume	[153]
German Society Anesthesiology and Intensive Care Medicine	2017			Isotonic with 1–2.5% glucose at 10 mL/kg/h	Isotonic with 1–2.5% glucose repeat boluses 10–20 mL/kg			[154]

Preferred intravenous fluids for perioperative management in children. Available solutions vary by country (France: Polyionique: B66; Switzerland: Ringer Laktat mit glucose 1%; Belgium: Hartmanns Glucose 2.5%; Austria: ELO-PAED 1% glucose; Germany: Electrolyt Infusionslosung 148 Glucose 1%; Holland: Kidialyte; sodium chloride 6.429 mg, potassium chloride 0.298 mg, calcium chloride dihydrate 0.147 mg, magnesium chloride hexahydrate 0.203 mg, sodium acetate trihydrate 4.082 mg, glucose monohydrate 11.0 mg)

because large sodium loads are poorly handled by the immature kidney and there is a lack of good evidence. Several recent studies support the use of an intra- and postoperative IV solution containing close to physiological concentrations of sodium in children >6 months of age but there are fewer studies in children 0–6 months of age [132, 156, 157]. Mild hyponatremia (serum sodium 133 and 134 mEq/L) has been reported in 12% of 34 neonates (0–7 days old) after a range of neonatal thoracic and abdominal surgical procedures [158]. The neonates received boluses of 10 mL/kg of normal saline or lactated Ringer's solution with or without 1% dextrose after induction of anesthesia, in response to poor urine output, blood loss, or hemodynamic changes. However, the relationship between the change in serum sodium between postoperative and preoperative values and free water administration did not support a relationship ($r^2 = 0.14$) contrary to the authors' conclusions [158]. The serum sodium was not <130 mEq/L in any neonate nor did sequelae occur. Judicious use of lactated Ringer's solution and normal saline in this age group points to the need for serial serum sodium concentrations and avoiding excess fluid administration [52].

Blood volume is estimated as 90–100 mL/kg in preterm infants, 80–90 mL/kg in term neonates, and 70–75 mL/kg in infants >3 months of age. In cases of circulatory instability or blood loss, the goal of treatment is to restore and normalize the circulating blood volume rapidly. However, the choice of which fluid to use for volume expansion remains contentious. Anesthesiologists use intravenous balanced salt solutions to replace the initial blood loss in a 3:1 volumetric ratio in neonates; beyond that, a survey of French and British anesthesiologists confirmed that the vast majority use albumin to restore euvolemia [159].

Intraoperative Hypotension

Hypotension is common in sick neonates, especially preterm infants. The definition of hypotension is, however, ill-defined, especially in preterm infants. Systolic blood pressure (SBP) correlates poorly with systemic perfusion, and other measures of regional perfusion have been advocated. Echocardiography and assessment of SVC flow have been suggested and near-infrared spectroscopy (NIRS) may provide noninvasive real-time monitoring of cerebral and tissue perfusion in neonates [160]. There is a significant debate as to which fluid should be given to hypotensive infants: crystalloids, albumin, plasma, and gelatin-based substitutes are equally effective. Vasopressors may also have chronotropic and inotropic effects, which will have a complex effect on the neonatal circulation and not necessarily result in increased organ perfusion despite increased SBP. Newborns treated with dopamine have been shown to have the same mortality as those treated with albumin but have better SBP responses [161].

In most cases, fluid resuscitation should be undertaken with crystalloids that contain sodium in the range of 130–154 mmol/L. Some use physiologically balanced solutions such as Hartmann's solution, Ringer's lactate solution, or Plasma-Lyte 148 solution and some continue to use 0.9% sodium chloride. In the pediatric intensive care unit, a survey of physicians revealed that the preferred solution to treat hypotension in the presence of sepsis, trauma, traumatic brain injury, and acute lung injury was 0.9% saline, whereas for postoperative cardiac surgery it was 4% albumin—both fluids in a volume of 10 mL/kg [162]. In the operating room where repeated fluid boluses >10 mL/kg IV may be required, we avoid using 0.9% sodium chloride because of the risk of developing hyperchloremic non-anion gap metabolic acidosis.

Colloids

There is no evidence that colloids are superior to crystalloids in fluid expansion and resuscitation in neonates. Early volume expansion in preterm neonates, whether with colloid or crystalloid, has yielded no long-term improvement in either morbidity or mortality [163]. A meta-analysis of this subject by the Dutch Pediatric Society identified only one study in neonates that reported no difference in serious outcomes (death, intraventricular hemorrhage, or chronic lung disease) between albumin and crystalloid solutions, but did note less fluid retention in the crystalloid group at 48 h [164, 165]. They concluded that isotonic saline should be the first-choice fluid to treat hypovolemia and hypotension in neonates. When prophylactic intravenous fresh frozen plasma, gelatin, or glucose were compared in preterm infants (in a large RCT), early morbidity and mortality and developmental outcome at 2 years were similar [166, 167].

Some pediatric anesthesiologists limit the role of crystalloid to 30–40 mL/kg in neonates, expanding the circulation or treating oliguria from that point onward with a colloid, albumin being the first choice [159].

Albumin

Exogenous albumin solutions are biological products derived from pooled human donors. Many different types of commercial albumin solutions are available. They are either hypo-oncotic (4%), iso-oncotic (5%), or hyper-oncotic (20% or 25%) and contain variable electrolyte concentrations, with sodium concentrations ranging from 87 to 160 mmol/L and potassium concentrations generally <2 mmol/L [168]. In hypotensive preterm infants, 4.5% albumin was demonstrated to be more effective than 20% albumin. This suggests that the volume of albumin administered is more important

than its concentration to maintain or restore cardiovascular stability [169]. Side effects from albumin are rare; however, hemodilution with large amounts of albumin (25% hemodilution of the blood volume) may produce a hypocoagulable state through inhibition of platelet aggregation or heparin-like effects on antithrombin III.

Nonprotein Colloids

Hydroxyethyl starches (HES) are modified polysaccharides suspended in 0.9% NaCl, or more recently, a more isoosmotic solution. HES solutions expand the plasma volume with effects lasting 2–6 h and are made of concentrations of 3, 6, and 10% [170]. The high molecular weight/molar substitution HES solutions are associated with hypocoagulability due to the still-unknown effects on factor VIII, the von Willebrand factor, and platelets [171]. Adult studies suggest volume replacement with HES may be more risk than benefit but studies on the use of starches in pediatric patients, particularly those who are critically ill and/or have renal dysfunction, are lacking [172]. In an open-labeled study of neonates and infants undergoing major noncardiac surgery, morbidity, length of stay, and laboratory indices (coagulation studies) with HES and albumin were similar [173]. In neonates without cardiac, renal, or hemostatic abnormalities undergoing central-line placement, the use of 6% HES did not increase creatinine or bleeding when compared with neonates receiving an equal volume of 5% albumin [174]. However, no improvement in cardiac output could be shown in hypotensive neonates with low cardiac output states after the administration of HES, isotonic saline, or 5% albumin [174].

Gelatins are polypeptides produced by degrading bovine collagen, which have a short duration of action because of their rapid but transient passage into the interstitial space, rapid GFR, and enzymatic cleavage by proteases. The data supporting the use of gelatin in infants are limited. Animal studies that evaluated capillary leak in septic shock indicate that gelatin and HES actually maintain plasma volume more effectively than albumin.

Transfusion Triggers

Neonatal transfusion guidelines for neonatal intensive care (NICU) are based on guidelines for VLBW infants as there is limited evidence specifically for full-term infants. There are no prospective studies in neonates that describe perioperative transfusion triggers, but transfusion thresholds during the first 2 weeks postnatal age are shown in Table 8.8. Transfusions in VLBW infants have been associated with BPD, NEC, IVH, and ROP, and neurocognitive changes in some studies warranting careful choice of the indications for transfusion in this age group [175, 176]. The threshold for red cell transfusion varies internationally as do the timing of the transfusion and "top-up" doses. In VLBW infants, physiologic anemia may reach a hematocrit of 24%, prompting interest to transfuse these infants. However, during the first month of postnatal life, the erythropoietin levels in these infants are two-thirds of adult levels despite the presence of anemia [177]. Transfusions have been administered to VLBW infants in the first 2 weeks of life to correct the anemia, but these are not without complications [177]. A systematic review reported that whether erythropoietin was administered before or after postnatal day 8, it did not reduce the transfusion rate and actually increased the risk of retinopathy of prematurity in those who received it [177]. Several studies that examined the immediate and long-term outcomes after restricted or liberal transfusion practices in VLBW infants yielded similar results [176]. However, a recent MRI study of brain volume in graduates of the NICU who received either restricted or liberal transfusions reported a disturbing finding: less cortical and subcortical white matter volumes in females who received liberal blood transfusions [178].

Table 8.8 Transfusion triggers in neonates

Postnatal age	Transfusion threshold (g/L)		
	Artificial ventilation	Receiving oxygen/ CPAP	Not receiving oxygen
First 24 h	<120	<120	<100
1–7 days	<120	<100	<100
8–14 days	<100	<95	<75–85
>15 days	<85	<85	<85

Large volume transfusion (defined as a circulating blood volume of a neonate in 24 h), or 50% of the circulating volume within 3 h, may occur in some high-risk surgery such as NEC. In situations where >40 mL/kg blood loss occurs, premixing the packed red blood cells with fresh frozen plasma may be appropriate [179]. Perioperative transfusions should be considered in neonates if:

i. Acute blood loss >10% of the circulating blood volume;
ii. Hemoglobin <80 g/L in a stable neonate with symptoms of anemia (including apnea, bradycardia, poor weight gain); and
iii. Hemoglobin <120 g/L in an infant with respiratory distress syndrome or congenital heart disease.

Postoperative Fluid Maintenance

With their revision of the approach to fluid administration in the intraoperative period, Segar and Holliday reduced the incidence of perioperative hyponatremia [180].

However, postoperative hyponatremia occurred [181] in part, because surgeons administered hypo-osmolar IV fluids and with the multiple stimuli that upregulated ADH release [35]. Subsequently, Segar and Holliday revised their postoperative fluid guidelines to use isotonic or near-isotonic solutions but at half of the previously recommended rates, 2 mL/kg/h for the first 10 kg, 1 mL/kg/h for the next 10 kg, and 0.5 mL/kg/h for the remainder [180]. The neonatal surgical patient remains at risk for increased ADH, given that pain, stress, narcotics, hypovolemia, and/or hemorrhage are associated with the postoperative period [35]. Adequate analgesia and control of the stress response in children is insufficient to downregulate ADH release [138]. Non-osmotic stimuli of ADH secretion include positive pressure ventilation, stress, nausea and vomiting, hypoglycemia, fever, and decreases in intravascular volume as a sequelae of illness or surgery (Table 8.1). Asphyxiated infants may have increased circulating arginine vasopressin (syndrome of inappropriate ADH, SIADH) and may be at increased risk of cerebral edema. Their fluid intake should be restricted for 48–72 h, i.e., ≤60 mL/kg/day, or until seizures are no longer considered a problem. Several studies have suggested that the use of isotonic saline solution decreases the risk of hyponatremia in sick children [130, 182]. Some surgical preterm neonates may require an additional 30 mL/kg/day because of increased insensible fluid losses and third space losses, and may also require additional sodium supplements (4 mmol/kg/day). Fluid management practices after surgery for congenital heart disease vary widely. The most common prescribed fluids are isotonic (mainly 0.9% saline) but hypotonic fluids are frequently prescribed. Most pediatric intensive care units limit fluid intake to 50% during the first 24 h post-cardiac surgery. The most frequently used fluids for resuscitation is 0.9% saline (44%) or colloids (27%).

It is a common practice to resume TPN in neonates with a dextrose, electrolyte, amino acid, and lipid infusion after surgery at 60–70% (usually 100 mL/kg/day) of the preoperative rate, with frequent serial monitoring of the serum electrolyte concentrations to preclude hyponatremia. Many postoperative infants gain considerable weight due to capillary leak and fluid administration in the perioperative period compromising respiration. Once the preterm infant with BPD is hemodynamically stable, diuresis (sometimes preceded by an infusion of albumin) is necessary to improve respiratory function and facilitate extubation of the trachea. Institution of TPN is one of several factors that has improved morbidity and mortality in preterm neonates after surgery for congenital bowel defects such as jejunoileal atresia [183]. Fluid restriction as described below for postoperative management after cardiac surgery may also be salutary in preterm infants with BPD.

Postoperative Metabolic Needs

The stress response in full-term and preterm neonates differs both quantitatively and qualitatively from that of adults. The increases in stress hormones associated with surgery in the neonate exceed those measured in children and adults but under most circumstances return to baseline by 24 h [184]. Neonates <48 h old have a diminished stress response compared with older neonates. One possible explanation for the latter difference may be the greater secretion of endogenous opioids in the perinatal period blunting the endocrine and metabolic responses [185, 186]. Resting energy expenditures increase by only 20% in neonates undergoing major surgery but return to normal values within 12 h. It has been suggested that one reason critically ill neonates fuel the metabolic stress response without increasing their resting energy expenditure is that, unlike adults, neonates are still actively growing. Only approximately 65% of neonatal energy requirements are necessary to meet resting energy expenditure. The remainder is directed primarily to maintain growth and to a lesser extent to regulate temperature and meet the demands of other activities. The total energy needs of intravenously fed, full-term, surgical neonates are about 85 kcal kg/day. Sick neonates stop growing, become lethargic, and require nursing in a thermoneutral environment. Thus, energy is available to supply the metabolic response to injury without any fluctuation in the resting energy expenditure. Other factors such as sedation may further reduce the resting energy expenditure, apportioning more energy for the metabolic response. This suggests that the routine administration of excess calories may not be warranted in critically ill surgical neonates and also supports the hypothesis that neonates redirect energy, normally used for growth, to fuel the stress response [187].

Special attention must be directed to providing optimal metabolic care in the postoperative period. Rates of survival for extremely low birth weight (ELBW) (<1000 g) infants have improved but delayed-onset growth failure is nearly universal. At the time of birth, only about 18% of ELBW infants are less than the 10th percentile for weight and length. At 36 weeks corrected gestational age, as the neonates near discharge from the NICU, most ELBW infants are less than the 10th percentile for weight and length. A 26-week gestation 1000-g birth-weight infant begins with body protein stores of approximately 88 g compared with 250 g in a full-term infant. Without protein intake, the infant loses approximately 1.5% of total body protein per day. After only 3 days without protein intake, body protein stores are reduced by 5% from birth and are 10% less than a fetus of comparable age. In contrast, after birth, most of the very preterm infants are fed more lipid and glucose and fewer amino acids and protein than they need. Not surprisingly, therefore, very preterm infants accumulate fat but remain relatively growth

restricted at term gestational age compared with those infants who grew normally in utero, and this postnatal growth restriction has long-term adverse growth, development, and health consequences.

Special Cases: Cardiac Surgery

Infants undergoing neonatal cardiac surgery require special consideration and are an exception to the above recommendations. The optimal maintenance fluid infusion rate is often less than has been outlined above to manage borderline ventricular function or excessive pulmonary blood flow [51, 188]. Similarly, intraoperative fluids must be reduced as fluid overload and renal dysfunction may significantly contribute to morbidity, e.g., after arterial switch surgery in neonates and infants [189, 190]. Furthermore, the use of intraoperative balanced salt solutions that contain glucose during pediatric cardiac surgery remains controversial because of possible associations with worsened neurological injury compared with results when glucose was not added. The use of glucose-free, balanced salt solutions during pediatric cardiac surgery, however, may result in hypoglycemia during the pre-bypass period. Moderate intraoperative glucose administration (2.5 mg/kg/min) will not cause major hyperglycemia but just may prevent episodes of hypoglycemia. Tight glycemic control in pediatric cardiac surgery may result in a 3% incidence of severe hypoglycemia, which highlights the need to monitor blood glucose concentrations during neonatal cardiac surgery to preclude swings in the plasma glucose concentrations [191].

Postoperative fluid restriction has also been widely accepted as one of the important strategies to reduce the risk of pulmonary edema and to improve respiratory function, prevent intravascular volume overload, and reduce multiorgan dysfunction early after pediatric cardiac surgery, especially in low-weight infants [192]. After cardiopulmonary bypass, sodium and water may be retained in response to the systemic inflammatory response to bypass and surgery that increase capillary permeability. Excess postoperative fluids after cardiac surgery correlate significantly and independently with prolonged mechanical ventilation and poor outcomes [193, 194]. For bypass cases, fluids are restricted to 50% of maintenance rates in the immediate postoperative period, whereas in non-bypass cases, it is limited to 60% of maintenance rates. This fluid regimen should continue until the infant's airway is extubated, after which the fluid rate is increased by 10% per day [194, 195].

Growth failure and malnutrition are common in neonates with congenital heart disease. The etiology of the growth failure is multifactorial and most likely reflects a hypermetabolic state, inadequate caloric intake, malabsorption, and genetic factors [196]. Fluid restriction used for hemodynamic management may also be a contributory factor. Congenital heart disease increases cardiac and respiratory work to a significant effect immediately after cardiac surgery. Adequate enteral nutrition may be difficult to achieve early after cardiac surgery in neonates, but it is essential for growth, wound healing, and the integrity of the immune system. Children with less complex cardiac lesions (e.g., VSD) may need up to 50% more calories than healthy infants to continue along a normal growth curve. Infants with single-ventricle repairs and aortopulmonary shunts may experience splanchnic ischemia due to the diastolic runoff from the shunt and are predisposed to NEC. In most cases, infants who require neonatal surgery have substantive difficulty in gaining weight postoperatively despite these adjustments to the caloric intake. Strategies to optimize the caloric intake and promote weight gain include the use of TPN in the early postoperative period, the institution of nasogastric feeds, and the use of high-calorie enteral feeds [197].

Temperature Homeostasis

Core body temperature in adults is maintained constant (±1.0 °C) within the body [198]. Temperature receptors located in the skin and deep structures detect changes in temperature (±0.4 °C) that are transmitted through the spinal cord to the preoptic nucleus of the hypothalamus. The hypothalamus responds by activating autonomic and behavioral changes to preserve core temperature. The skin contributes between 20 and 50% to this response [199]. An active precapillary vasodilation sweating, arteriovenous shunt vasoconstriction, and shivering are the primary autonomic thermoregulatory mechanisms to maintain a constant core temperature between 36 and 37 °C in humans [198, 199].

Heat loss in neonates occurs by four distinct mechanisms: radiation (39%), convection (34%), evaporation (24%), and conduction (3%) (Fig. 8.6) [200]. Neonates have a large area/body mass ratio and less subcutaneous fat (less than half that compared with adults), greater body water, and immature skin, and hence they lose body temperature quickly [201]. The normal body temperature in the neonate ranges between 36.5 and 37.5 °C. Neonatal hypothermia is divided into three categories: mild or cold stress, 36–36.4 °C; moderate stress: 32–35.9 °C; and severe stress, <32 °C [201, 202]. The thermoneutral zone, defined as the ambient temperature range that does not require energy above the basal metabolic rate to maintain, in the adult is 26–28 °C, whereas in the naked term neonate it is 32—35 °C and in the preterm infant 35 °C [201]. Two-thirds of the neonate's heat production is devoted to basal metabolism, reducing the amount of energy available to protect from cold stress [186]. A naked full-term neonate, with no thermal protection exposed to an ambient temperature of 25 °C, may lose up to 100 cal/kg/min, a

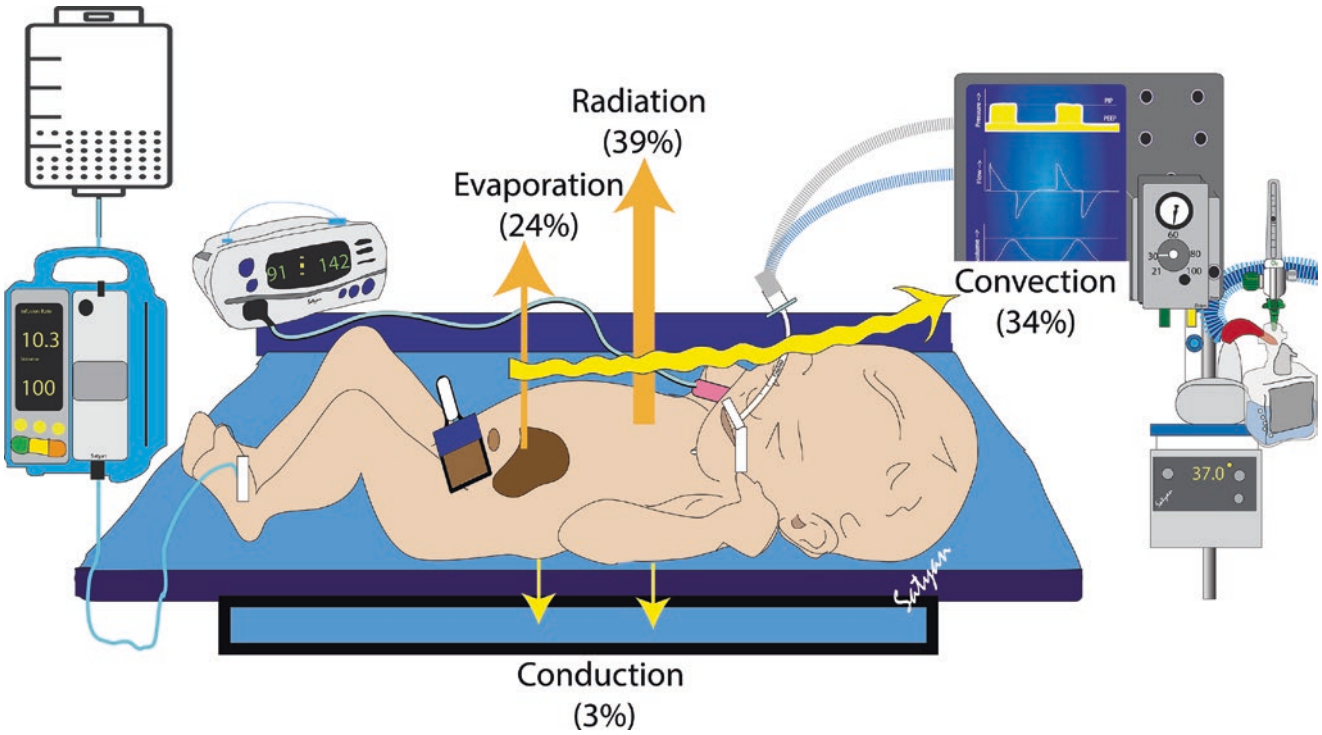

Fig. 8.6 This diagram illustrates the four mechanisms of heat loss in neonates: radiation (39%), convection (34%), evaporation (24%) and conduction (3%). Effective strategies to mitigate these losses in most neonates include heating the operating room (to 28 °C) before the neonate's arrival and the use of a forced air warmer

decrease in core temperature by 2 °C, and a decrease in skin temperature by 4 °C within 30 min [203]. In contrast, a warmed baby loses only 22–28 cal/kg/min in the same conditions [204].

Brown Adipose Tissue (BAT)

Brown adipose tissue (BAT) develops between 26 and 30 weeks gestation and is the major energy source for heat production in the neonate [205, 206]. Its brown color stems from the concentration of mitochondria within the tissue. BAT accumulates in discrete areas including the interscapular, para-aorta, and perirenal/adrenal regions beginning mid-gestation in the neonate, ultimately constituting about 5% of the neonate's weight at term [207, 208]. BAT is highly vascular, and innervated with noradrenergic fibers. Heat production produced from BAT, also known as non-shivering thermogenesis, is initiated by cold temperatures (≤23 °C in humans), which release norepinephrine [207]. Norepinephrine, the neurotransmitter primarily responsible for BAT, in turn, activates uncoupling protein 1 (located in BAT mitochondria membrane), which facilitates the transfer of protons generated by the electron transport chain to preferentially transfer them into the mitochondria, generating heat in the process, rather than allowing them to bind to ATPase and produce energy [207]. Other hormones are cofactors in activating non-shivering thermogenesis including thyroid hormone, cortisol, leptin, and prolactin. During the first 2 weeks of postnatal life, cold-induced non-shivering thermogenesis is replaced with shivering thermogenesis [209].

Preterm infants <30 weeks of gestational age have minimal BAT stores and thus cannot benefit from non-shivering thermogenesis to any large extent; as a result, they are at risk of hypothermia for several months after birth. Moreover, their glycogen stores are reduced. Heat loss via convection and conduction sources is increased in extremely low weight preterm infants because peripheral and arteriovenous shunt vasoconstriction is impaired in the first 12–24 h after birth. As a consequence, extremely preterm neonates may have peripheral temperatures that are warmer than their core temperature [210]. Evaporative heat loss is predominant during the first 10 days after birth in extremely preterm infants [211]. Preterm neonates have a thinner layer of keratin and little subcutaneous tissue, which predisposes them to increased heat loss through convective and evaporative mechanisms [201].

The cutaneous vasomotor regulation along with shivering are minimally active modalities in neonates. Sweating is impaired in the first 2 weeks after birth but could be activated for temperatures that exceed 37.9 °C [200]. Non-shivering

thermogenesis remains the primary mechanism for heat production in neonates and infants until 6–12 months of age [198, 205]. As the body temperature decreases to 35–36 °C, activation of the sympathetic nervous system initiates non-shivering thermogenesis, along with a small contribution from vasoconstriction to attenuate the decrease in temperature. Non-shivering thermogenesis triggers energy production from BAT [212]. However, with the limited stores of BAT, the source may become depleted within 24 h in a cold environment [204, 211, 213].

Normothermia and Hypothermia

Core and axillary temperatures between 36.5 and 37.4 °C are considered normal in neonates and infants. The differences in temperature between full-term and preterm neonates and between rectal and axillary temperatures are only several tenths of °C [214, 215]. Hypothermia has been defined as a core body temperature <36.5 °C, or a skin temperature <36 °C. Severe hypothermia occurs when the core and skin temperatures are <32 and <31.5 °C, respectively [212, 216, 217].

Hypothermia is a well-known independent risk factor of morbidity and mortality in neonates and infants [201, 212]. Cold stress at birth increases oxygen consumption by two- to three-fold (up to 15 mL/kg/min) [205, 217] and norepinephrine release by 2.5 times [198]. A decrease in body temperature of 1 °C increases mortality by four-fold, particularly in the preterm infant and those <1500 g [201]. Hypothermia has been linked to respiratory distress, metabolic derangements, intraventricular hemorrhage, major brain injury, bronchopulmonary dysplasia, retinopathy of prematurity, NEC, and nosocomial infection [212, 218, 219]. Hypothermia has also been linked to hemodynamic instability, increased blood loss, and decreased metabolism of propofol and muscle relaxants. However, transient mild intraoperative hypothermia may not be harmful to the neonate [220].

Prevention of Hypothermia in Infants Receiving Anesthesia

Anesthesia decreases vasoconstriction and shivering thresholds by up 2 °C but has little effect on sweating [198]. General anesthesia, both intravenous and inhaled, abolishes non-shivering thermogenesis and has little effect on the peripheral vasoconstriction threshold in neonates [221, 222]. Curiously, in vitro studies demonstrated a dose-dependent suppression of BAT activity with inhaled agents, but not with propofol or ketamine [223].

Temperature decreases in the first 10 min after induction of anesthesia due to a redistribution of central core heat to the periphery. The core temperature decreases approximately 0.5 °C during the first 45 min of anesthesia but can be 1.5 °C less by the end of the surgery without corrective interventions [220, 224].

Table 8.9 Strategies to prevent hypothermia in neonates during surgery and MRI

• Keep the neonate warm, particularly before transport and MRI
• Warm the operating room before arrival, ideally to 26–28 °C
• Activate a forced-air heater (not MRI-compatible) using an approved total body blanket for infants to 43 °C before the neonate arrives in the suite. Use for all procedures.
• Warm disinfectant solutions when possible
• Warm fluids particularly if a large volume of IV fluid is anticipated and warm all blood products (except platelets)
• Humidify inspired gases where possible
• Keep the skin dry
• Keep the operating room warm until the neonate is fully draped
• Monitor the core temperature of the neonate before, during, and after surgery or MRI
• Reduce the room temperature for surgical comfort after draping, to ≥21 °C
• Increase the operating room temperature to 26 °C before undraping the neonate
• Cover the head, particularly preterm babies
• Use the thermoneutral incubator, warming packs during transport and ensure it is warm before transferring the patient

In the NICU, the use of a radiant warmer, overhead heat lamps, polyethylene wrap/vinyl bag/thermal mattress, and prewarmed transport incubator prevents hypothermia. Additional techniques may include exothermic warming mattress, heating humifying inspired gases, along with occlusive wraps and radiant heat, and warmed polyethylene caps, which are also useful (Table 8.9) [201, 212, 225].

In the operating room, two primary strategies prevent the neonate from becoming hypothermic, and several secondary strategies may also be used [219]. The first one is to preheat the operating room temperature to ≥26 °C before the neonate arrives. This attenuates but does not preclude hypothermia from developing [220, 222]. An operating room temperature of 30 °C may prevent a decrease in the internal temperature of 7.7 °C/h in a low-birth-weight neonate, whereas a forced-air device at 38 °C may prevent a decrease of 5.0 °C/h. In the same clinical scenario, a mattress warmed at 39 °C prevents a decrease of 1.5 °C/h, and the head tube gauze only prevents a 0.4 °C/h. When combined, these measures may decrease the heat loss in a model of the neonate, almost four-fold less than in a naked full-term neonate [226].

The second strategy is to use a forced-air body warmer under the neonate, prewarmed to 40 °C before the neonate arrives in the operating room and maintained throughout induction of anesthesia and patient positioning, until the surgical drapes are applied. A forced-air warmer is the single most effective strategy to maintain normothermia in the neonate [226–229]. Warmed intravenous and irrigation fluids are

secondary strategies especially with high flow infusions or extensive peritoneal lavage, although most fluid warming strategies are impractical in neonates due to the large dead space of the warming devices. Other secondary strategies including using humidified gases in the ventilator circuit, a radiant overhead warmer, and covering the neonate (during the first 20 min of anesthesia) reduce heat loss [224, 230, 231]. Once the surgical drapes have been applied, the temperatures of both the operating room and the forced-air warmer may be adjusted to maintain thermoneutrality in the neonate and avoid hyperthermia [229].

The type of surgery and the ambient operating room temperature are key determinants of the severity of the hypothermia that may occur intraoperatively [224]. Neonates and infants undergoing cardiac, urologic, and ENT procedures are at the greatest risk for hypothermia [232].

In contrast to adults whose temperature is only monitored for procedures that exceed 30 min in duration, the temperature of all neonates and infants should be monitored continuously [233, 234]. Nasopharyngeal, esophageal, rectal, and bladder are all useful measurements sites [230, 234]. Esophageal temperature probes placed retrocardiac accurately monitor core body temperature. Nasopharyngeal temperatures are similar to esophageal measurements, particularly if there is no leak around the tracheal tube [235]. Rectal temperature may be an effective site to monitor temperature although it may fail to track temperature changes if the probe is embedded in feces. The urine output may influence the temperature measurement measured in the bladder when a vesical catheter is used [230]. Axillary temperatures properly positioned (adjacent to the axillary artery) tracks the core temperature [236, 237], although all too often the tip of the probe extends beyond the axilla in neonates and tracks the temperature of the air from the forced-air heating blanket rather than the neonate.

Transport is a critical period during which the neonate may become hypothermic. As many as 50% of neonates who are transported from the NICU to the operating room or MRI return with a rectal temperature <36.5 °C [238]. The implementation of a standardized protocol includes the use of thermoneutral incubators, portable-heated mattresses, an occlusive wrap, an exothermic mattress, and warmed cap and temperature monitoring before and after the transport decreases the frequency of hypothermia by as much as fourfold [201, 218, 232].

Temperature control during MRI is particularly challenging. The magnet in MRI scanners is maintained in a cool environment with high humidity, which may cause significant radiant and convective heat losses in the neonate. However, most MRI scans can be performed in neonates during natural sleep or with chloral hydrate, without the need for general anesthesia. In these circumstances, the majority of neonates maintain a normal rectal temperature (defined between 36.0 and 37.5 °C), even after 80 min [239]. However, episodes of hypothermia have been reported, particularly in infants whose pre-scan body temperature is below normal [238, 239].

MRI scanners produce radiofrequency radiations between 64 (1.5 Tesla) and 128 MHz (3 Tesla), which may be absorbed by the neonate, increasing their body temperature and, if it continues for a protracted period, overheating them [239]. Hyperthermia has been associated with cellular and organ damage, possible developmental abnormalities, and prolonged intubation, which should be avoided. MRI scans in infants should be maintained below the maximum allowable specific absorption rate (SAR) of 4 W/kg to reduce the risk of overheating [240]. Few studies in older children confirm that the body temperature increases from 0.2 to 0.5 °C during MRI scans [241].

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9 General and Thoracoabdominal Surgery Including Management of Conjoined Twins

Kate Cross, Peter Carachi, and Sally Wilmshurst

Introduction

Provision of safe anesthesia for the neonate undergoing thoracic or abdominal surgery presents several challenges for the pediatric anesthesiologist. This is a diverse group of patients, encompassing the robust term neonate presenting for elective inguinal hernia repair to morbidly sick extreme low-birthweight neonates with necrotizing enterocolitis. This group presents with a huge variation in size, from approximately 500 g to 5 kg, and in the maturity of organ systems. Some will be cared for at home, whereas others will be cared for in the neonatal intensive care unit (NICU). Several surgical specialties may be involved in the care of the neonate including cardiothoracic, general surgery, hepatic surgery, and urology.

Comorbidities are common in this age group. Congenital surgical lesions often coexist with other abnormalities such as congenital heart defects; other organ involvement, e.g. lung hypoplasia in congenital diaphragmatic hernia; and midline defects as in VACTERL, which is an acronym for vertebral, anal, congenital heart disease, trachea-esophageal fistula, renal, and limb defects. Medical complications of prematurity such as persistent pulmonary hypertension, respiratory distress syndrome, and hydrocephalus also need to be considered.

This chapter aims to briefly outline some of the main general issues, describe specific thoracic and abdominal conditions that require surgical or anesthetic intervention in the neonatal period, and describe the surgical and anesthetic requirements for each. There are very few randomized controlled trials to guide management. Most strategies are based on case reviews or expert consensus. A recent evidence-based guideline for full-term neonates undergoing intestinal surgery has been produced by the enhanced recovery after surgery (ERAS) group [1]. This is a first step towards improving the care provided to neonates who require intestinal surgery, and many of the principles can also be applied to preterm neonates, but the evidence for some aspects of care remains quite weak.

General Considerations

Anesthesia complications are more common in the neonatal period [2–4] and there remains concern about the safety of anesthesia on the developing human brain (see Chap. 18). For these reasons, only essential surgery should be carried out during this period. Wherever possible, this surgery should be carried out in specialist units. Antenatal identification of common or severe congenital abnormalities is usually very reliable in developed countries, ensuring that delivery and postnatal care can be optimally planned during the antenatal period. Acute surgical conditions and unexpected congenital anomalies can present to any hospital and may require that the neonate is stabilized and transferred to a specialist unit for further investigation and management.

Multidisciplinary collaboration between the anesthesiologist, surgeon, and, if relevant, neonatologist is vital to ensure the neonate is optimally prepared for surgery and has a safe postoperative plan.

Neonatal anesthesia requires several special anesthesia-related considerations:

- Immature organ systems, particularly the kidney, liver, and cardiovascular system
- Altered drug handling
- Rapidly changing fluid and electrolyte requirements
- Feeding issues
- Blood result reference ranges and significance
- Vascular access difficulties
- Regional anesthesia challenges
- Prone to heat loss and poor heat retention

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– Equipment difficulties such as ventilators and monitoring
– Postoperative apneas
– Parental anxiety

Preoperative Assessment

History and Examination

Evaluation includes a detailed history of gestational age, birth history, Apgar scores, issues in the perinatal and subsequent period, the surgical complaint, how the baby is feeding, known associated anomalies, administration of vitamin K, presence or need for vascular access, any relevant family history, and current medication history. It is useful to record how well very sick or small babies handle their daily cares as this can yield insight into how the neonate will tolerate transfer to theater, anesthesia, and positioning. If surgery is required in the first few days of life, the mother may still be hospitalized herself and unavailable to give a history. The father may be accessible to document the history and consent or surgery; otherwise, the information may be obtained by telephone.

The examination should be relevant to anesthesia and include an assessment of the airway, position of lines, and tubes (or potential sites for their insertion), fluid status, and an examination of the heart and lungs. The back and sacrum can be inspected if regional anesthesia or analgesia is planned. Cleft lip or palate, choanal atresia, or more challenging airway abnormalities such as Pierre-Robin sequence can sometimes coexist with midline congenital abnormalities (e.g., VACTERL).

Investigations

Congenital heart disease is more frequent in children with other congenital abnormalities; therefore, an echocardiogram should be performed preoperatively where possible. Abdominal ultrasound is useful to assess kidneys in the presence of esophageal atresia or other midline abnormalities. Cranial ultrasound may be performed in premature infants to diagnose an intracranial hemorrhage. Spinal imaging may be helpful if regional analgesia is planned.

For major surgery or in hospitalized infants, blood testing should include bilirubin levels, renal and liver function tests, full blood count, blood glucose concentrations, and the coagulation profile. Both the prothrombin time and APTT is commonly prolonged in premature neonates. The significance of this is unclear in the absence of bleeding. These results should be interpreted in the context of the lab standards for the hospital and in discussion with a hematologist and the anesthesia and surgical teams. The concentration of platelets is often low, or even if the concentration is normal, platelet function may be impaired in septic or sick neonates. Again the significance of the absolute number is unclear and should be managed based on the advice of the local hematologist, but most authorities would recommend transfusing platelets if the concentration is $<100 \times 10^9$/L [5].

A "group and save" (also termed a "group and reserve") should be prepared for all but the most minor surgery following local policies. If the need to transfuse packed red blood cells seems likely, then a crossmatch of 1 unit of packed red blood cells should be performed. Blood products should be available for moderate and major surgery, that is, safe in the presence of maternal antibodies. In practice, O-negative blood is often prepared for neonates as the red cells have no antigen surface receptors to react with circulating antibodies in the neonate.

Logistical Issues

Emergency Status

Some thoraco-abdominal surgery needs to be performed as an emergency, for example, gastroschisis, necrotizing enterocolitis with perforation, malrotation with ischemic gut, or tracheoesophageal fistula that requires ventilatory support. Other procedures can be delayed until the neonate is stabilized and a suitable theater slot is scheduled. These procedures include bowel obstructions or atresia without perforation, such as pyloric stenosis and anorectal malformation, congenital diaphragmatic hernia, and cystic lung malformations.

Surgery in the NICU

Transfer of the critically ill neonate to a distant operating theater, particularly extremely low-birth-weight [ELBW] infants, increases morbidity and mortality (see Chap. 13). It can also be technically challenging, especially if the neonate requires inotrope infusions or additional intensive care support such as HFOV or inhaled nitric oxide (iNO). In these situations, it is important to assess whether surgery should instead be carried out in the NICU. This was first described for PDA ligation and diaphragmatic hernia [6, 7]. It is now becoming commonplace for NEC surgery. The risk-benefit of surgery on the NICU varies from unit to unit depending on geography and personal preferences. Drawbacks and challenges of performing neonatal surgery in the NICU include maintenance of sterility, limited space, ensuring adequate access to the neonate during surgery by the whole team, unsuitable lighting, anesthesia monitoring, the availability of drugs, and equipment, temperature control, privacy, and in some centers, enlisting the support of the NICU personnel. Most of these issues can be addressed through good communication, advance planning, and the use of locally agreed upon protocols among the NICU, surgical, and anesthesia teams. Simulation exercises with a setup plan and designated equipment trolley can help

defuse obstacles, addressing practical issues and engaging the whole team's participation [8]. A team brief should always be performed preoperatively and should include members of the NICU team. Surgical and anesthesia consents should be obtained and the child's ID confirmed as is standard local practice. The availability and location of blood should be checked before induction of anesthesia; a person should be designated to collect the blood from the blood bank (particularly after hours when minimal staff is present). All blood products (see below) should be checked in the standard manner according to hospital guidelines. A standard blood warmer requires a large volume for priming and is inappropriate for small volume transfusions as in the case of a neonate. Accordingly, we filter 10–20 mL aliquots of blood through small volume blood filters (Hemo-Nate® blood filter, Utah, Midvale UT, USA) and either immerse the sealed syringes in a warm water bath or warm them before use.

Anesthesia machines and scavenging equipment are rarely available in the NICU. Consequently, an intravenous anesthetic technique is usually favored, which complements existing sedation/analgesia and paralysis strategies as well as sidestepping the issue of neurocognitive effects of anesthetics on the neonatal brain. Standard monitoring including end-tidal or transcutaneous CO_2 if oscillated should be functional. Before the neonate is draped, the anesthesiologist should ensure lines are accessible to administer medications, the monitoring is optimal, and that they are familiar with the ventilator and syringe pumps before starting.

Team Brief and Preparing the Theater

A team brief should be performed for all cases including emergencies and regardless of the operating location [9]. The theater should be pre-warmed to ~80 °F (or 27 °C). Thought should be given to the necessary anesthetic and surgical equipment, surgical access, positioning, and warming the baby using forced-air warming during surgery, fluid warming, and insulating wrapping material. Red blood cells and blood products should be available in a nearby refrigerated location if required.

Conduct of Anesthesia

Sedative premedication is rarely used in neonates. Occasionally glycopyrrolate or atropine may be useful if a difficult airway is anticipated or if the use of the bronchoscope is planned although this practice has fallen by the wayside in many centers; in North America few administer prophylactic anticholinergics unless IV succinylcholine is planned.

Monitoring

Standard intraoperative monitors should be used following national standards. Obtaining reliable cardiorespiratory values before induction of anesthesia may be a challenge in the neonate who is constantly moving. After induction of anesthesia and tracheal intubation, noninvasive blood pressure, ECG, capnography, and hemoglobin saturation are recorded. The skin can be easily damaged by adhesives used in monitoring. End-tidal CO_2 monitoring should be used except when HFOV is used; in the latter case, transcutaneous CO_2 is preferred (see Chap. 7). Pre- and post-ductal saturations are helpful in the presence or suspicion of congenital heart disease or persistent pulmonary hypertension. Invasive monitoring can be considered for major surgery or in the presence of congenital heart disease, sepsis, or when frequent blood sampling is needed. Umbilical lines may already be present in a neonate whose lungs are ventilated. These vessels can be useful for up to 5 days postnatally, although they are prone to disruption during abdominal surgery. If used, the tip of the UAC optimally should be located above the diaphragm at the T6–10 level and the UVC at the SVC/RA junction. Arterial lines in neonates carry a significant risk of limb ischemia, thrombosis, or long-term limb length discrepancies. For this reason, they should only be used when clinically indicated and the risks and benefits discussed with the wider team and the parents (see Chap. 7).

If accessible, capillary refill can be regularly assessed during surgery. Bowel discoloration may be a sign of tissue hypoperfusion. Near-infrared spectroscopy (NIRS) is increasingly used in neonatal cardiac surgery and can also be useful for monitoring cerebral and mesenteric perfusion in the NICU, although access to the abdomen would be limited during surgery [10, 11]. Monitoring urine output can be useful during long surgery although the neonate may not make urine for the first 24 to 48 h after birth. If the neonate is making urine, the volume could be monitored although it is usually very small, and technically, measuring the volume can be difficult or impossible during certain surgeries such as bladder exstrophy.

Induction

Tracheal intubation is mandatory for neonates who require thoracic and abdominal surgery. Laryngeal mask airways (LMA) are rarely used in neonates, although they may be useful for rescuing a difficult airway or for bronchoscopy. Obtaining and maintaining a good seal around the larynx is difficult, although the I-gel™ LMA was effective during neonatal resuscitation [12] and comparable to the Proseal 1 during anesthesia [13]. However, most have frequent difficulties seating the LMA, maintaining a patent airway, as well as challenges ventilating the lungs with sizes 1 and 1.5 LMAs [14, 15]. Since most surgery in neonates is emergent, a tracheal tube is the most appropriate airway.

A feeding tube should be inserted into the stomach in neonates with full stomachs, or if an indwelling feeding tube is already present, it should be aspirated after rolling the neo-

nate to the left and right lateral decubitus positions while aspirating the stomach contents. In some circumstances, it may be necessary to remove the feeding tube to facilitate laryngoscopy. It should be replaced once the airway is secured.

Where possible the neonate should be oxygenated before induction of anesthesia. It is often quite challenging to hold a facemask in place with a crying neonate. Not infrequently, neonates desaturate during laryngoscopy and intubation despite our best efforts to pre-oxygenate, even in those with normal airways [16]. To minimize the risk of desaturation, care should be taken to maintain preexisting CPAP or PEEP, to gently mask ventilate the lungs after induction of anesthesia, or to apply high-flow nasal oxygen during laryngoscopy to prevent desaturation [17, 18].

An intravenous or inhalational induction may be used in neonates. An inhalational induction is very rapid in the neonate, but increases the risk of aspiration if a full stomach is present, as is often the case in neonatal surgery. Nonetheless, some centers routinely perform inhalational inductions in neonates even full stomachs without complications [19, 20]. Inhalational inductions are useful when intravenous access has not been established before induction of anesthesia or a difficult airway is suspected. An intravenous induction is often more appropriate in neonates, but care should be taken to give the agents slowly and titrate to effect wherever possible as even propofol has resulted in several case reports/series of profound bradycardia and hypotension at induction in neonates [21]. It must be appreciated that neonates, particularly VLBW infants, who are nursed in the NICU are managed relatively "dry" to reduce the risk of home discharge on oxygen, intraventricular hemorrhage, necrotizing enterocolitis, and patent ductus arteriosus [22, 23]. However, when general anesthesia is induced in such neonates, hypotension may ensue [24]. Accordingly, neonates should be pretreated with 10–15 mL/kg balanced salt solution before induction of anesthesia to attenuate any decreases in blood pressure with induction of anesthesia [25]. For those neonates who have been receiving sedative medications in the NICU, supplemental boluses of the same sedatives may be sufficient to achieve a surgical depth of anesthesia.

A classic rapid sequence induction may be an unsuitable technique for neonates due to the speed they desaturate during apneic periods and the compressibility of the cricoid ring when pressure is applied. Consequently, a "modified rapid sequence induction" includes gentle mask ventilation during induction of anesthesia, maintaining a low peak airway pressure to avoid gastric insufflation until the airway has been secured with a tracheal tube and avoiding cricoid pressure [17, 26–29]. An alternative to gentle mask ventilation may be the use of "high-flow" nasal oxygen (at 8 L/min flow) to preclude desaturation during tracheal intubation; the results of this study are pending [30].

Vascular Access

Choose a site and size of vascular access that is most appropriate to the surgery. Venous access may already be present in neonates who are nursed in the NICU, but small size catheters such as a 24 gauge, while adequate for use in the NICU, may be inadequate in the operating theater if the need arises to rapidly transfuse packed red blood cells, to resuscitate large volumes of fluids/albumen, and/or to sample blood. Larger size venous access such as a 22 gauge or central line should be established if transfusion is a possibility. Venous access in the lower extremities is not uncommon in neonates as the saphenous vein is substantial, although in some circumstances, intra-abdominal surgery, in which the vena cava or a tributary must be compressed or ligated, may render IV access in the lower extremities useless.

Femoral and jugular lines size 4 or 5F are appropriate for central venous access but surgical positioning may influence this choice. Caution should be exercised in neonates with congenital heart disease as a shunt (e.g., Blalock) may be present from previous surgery or a left-sided SVC can directly communicate with the coronary circulation.

Ultrasound will identify patent central veins for cannulation [31] and an interventional radiologist can often assist with difficult access. If long-term vascular access is required for parenteral nutrition or antibiotics, a peripherally inserted central catheter (PICC) or midline catheter should be considered under the same anesthetic.

Temperature Monitoring and Warming

Neonates are poikilotherms with limited ability to generate heat in a cold stress environment. They depend on norepinephrine-mediated non-shivering thermogenesis via brown fat to keep warm (see Chap. 8). To maintain normothermia, neonates should be nursed in a thermoneutral environment between 36.3 and 37.3 °C [32]. Prolonged abdominal and thoracic surgery, during which body cavities and viscera are exposed, is associated with profound heat loss in the neonate unless preventative measures are taken. It should be noted that an under-appreciated period when heat loss can occur is during transport from the NICU to the operating theater. Up to 50% of neonates who are transported from the NICU to MRI experience temperatures <36.5 °C (see Chap. 8). The use of heating pads in the transport incubator may offset heat loss during transport [33]. Active warming strategies should be incorporated in the operating theater protocol for neonates to prevent hypothermia from developing. Such strategies should include preheating the operating theater (to 80 °F or 27 °C) before the neonate arrives; the use of a forced-air warming blanket, heating fluids, and blood; use of a heat moisture exchanger in the ventilator circuit; and insulating the head and body parts to minimize heat loss. Surgical irrigation fluids should be warmed and exposed bowel covered with warm wet towels

whenever possible [34]. Core temperature is the preferred temperature metric, although the choice of location depends on factors such as the site of surgery and patient issues such as the presence of an imperforate anus or other anomaly. Core temperature is most reliably monitored in the neonate in the esophagus (retrocardiac) or nasopharynx.

Positioning

Positioning depends on the surgical access required, including the prone or lateral position. Pressure areas need particular care and attention before commencing surgery and at regular intervals during prolonged surgery. Also, care should be taken to prevent accidentally leaning on the neonate.

Fluid Management

Managing fluids in the neonate and particularly in the premature neonate is an area of ongoing debate (see Chap. 8). Controversy exists regarding the choice of fluid; balance salt solutions are used for most fluid replacement intraoperatively, contrasting with albumin, which is widely used in the NICU. The reason for avoiding albumen is that it may worsen postoperative edema [35]. Most techniques to monitor fluid management in adults and larger children such as cardiac output monitoring, echocardiography measurements, and esophageal Doppler are neither sufficiently miniaturized nor validated for use in neonates [36]. Surrogate markers of volume status such as heart rate, blood pressure, central venous pressure, capillary refill, base deficit, lactate, and urine output are widely used instead, although none provide an entirely accurate assessment of tissue perfusion.

Fluid requirements in the perioperative period can vary from trivial to massive. Fluid management should identify and correct the preoperative fluid deficit, continue maintenance fluids and electrolytes, replace perioperative losses (which can be considerable in thoracic and abdominal surgery), and optimize cardiovascular stability and blood sugar management.

Deficit

Neonates nap 1–3 h at a time, after which they feed for 1–2 h. This cycle continues for the first 4–8 weeks after birth. Current preoperative fasting guidelines permit clear fluids 2 h preoperatively, breast milk 4 h, and formula 6 h. Although some advocate a preoperative fast of 1 h after clear fluids to preclude prolonged fasts [37], such a proposal has no traction in neonates as their nap times and feeding regimens preclude accumulating a fluid deficit. For neonates nursed in the NICU, continuous IV fluids avoid developing significant preoperative fluid deficits. A sick, unstable surgical neonate or one with a delayed surgical presentation may present with a large deficit and require resuscitation with 10–20 mL/kg (NICE) aliquots of a balanced salt solution such as Ringer's lactate to restore euvolemia.

Maintenance Requirements

The maintenance fluid requirements depend on the age of the neonate. Insensible losses are greater in premature infants than in full-term neonates and infants for several reasons: in premature infants their skin is thin (with minimal subcutaneous fat), and they have a large body surface area to volume ratio, ventilator requirements, and warming, which lead to greater maintenance volumes. Serum ADH is increased, GFR is reduced, and urine concentration is limited by immature renal tubular function early in the life of the neonate. Fluid and sodium requirements are least during this time (60% of normal) and dextrose-containing fluids are appropriate to prevent hypoglycemia, especially in premature infants. Sodium is added to the fluids after the first few days of life and the volume of fluids administered is liberalized once the postnatal diuresis occurs [38–40]. Maintenance fluids can be continued perioperatively using a syringe driver or mechanical pump for precise delivery. In some neonates and most premature infants, the maintenance solution for neonates in the NICU consists of an electrolyte solution that includes calcium and 10% dextrose to prevent hypocalcemia and hypoglycemia. These solutions are infused at a volumetric rate of 4 mL/kg/h for the first 10 kg [41].

Managing glucose-containing solutions during neonatal surgery has been controversial. Some clinicians continue the preoperative maintenance infusion rate out of fear that reducing the rate may lead to hypoglycemia during the perioperative period (from increased circulating insulin levels), whereas others reduce the infusion rate to limit the hyperglycemic response to the stress of surgery. Although there has been a dearth of evidence published to date on this issue, one recent retrospective study reported that the postoperative glucose concentration in neonates within 4 h of surgery after an intraoperative glucose infusion of 8.2 mg/kg/min was 80% greater than that in neonates whose glucose infusion was 15% less, or 6.9 mg/kg/min [42]. To further define the frequency of postoperative hyperglycemia, a retrospective review concluded that reducing the infusion rate of glucose-containing maintenance solutions in neonates by 50% intraoperatively (from 7.3 to 3.75 mg/kg/min glucose) decreased the risk of postoperative hyperglycemia without changing the risk of hypoglycemia [43]. If the glucose infusion rate is decreased during surgery, we strongly recommend that the serum glucose concentration be measured serially.

Perioperative Losses

Perioperative fluid losses can range from minimal as in a straightforward surgery such as hernia repair to considerable during bowel surgery in which the bowel is exposed for long periods. Large perioperative fluid losses require balanced salt solutions such as lactated Ringer's solution up to volumes of 50–75 mL/kg. Although volumes as large as 100 mL/kg may not be unusual in this setting, these large volumes

may herald the onset of a dilutional coagulopathy, notably thrombocytopenia and possibly coagulation factors. Furthermore, premature infants are often hypoalbuminemic prompting the administration of 5% albumin once 50–75 mL/kg balanced salt solutions had been infused. In some institutions, colloid is only introduced if normovolemia cannot be achieved with these balanced salt solutions and blood products are not indicated.

Glucose

Neonates, particularly those with limited hepatic glycogen stores, are at risk of hypoglycemia. The latter is exacerbated by prematurity, stress, asphyxia, maternal diabetes, or the presence of certain syndromes such as Beckwith-Wiedemann or hyperinsulinism. Dextrose-containing fluids should be considered for all neonatal surgery, avoiding hypotonic fluids after the first few days of life. Neonates from the NICU often present with a dextrose maintenance infusion at the time of surgery, whereas neonates who arrive from home may not have an IV. In the absence of an appropriate commercial glucose-containing balanced salt solution, we prepare a 2% glucose-containing lactated Ringer's solution by adding 4 mL of D50W to 96 mL of lactated Ringer's solution in a Buretrol [44]. Blood sugar should be closely monitored as levels below 2.6 mmol/L (47 mg/dL) for a prolonged period and hyperglycemia are both associated with neurological injury and poor outcomes [45].

Transfusions

Estimated neonatal blood volume is 90 to 100 mL/kg in the preterm neonate and 80–90 mL/ kg at term. Although in 2014, the literature recommended transfusion in the NICU when 10% of blood volume is lost or where Hb is <90 g/dL in an otherwise well neonate or <110 g/dL in a neonate with congenital heart disease or respiratory distress [46], since then the transfusion threshold in neonates has become less clear. Several studies in VLBW neonates (including ETTNO and TOP trials) demonstrated that blood transfusions in this age group based on restrictive (7–8 g/dL) or liberal (9–12 g/dL) thresholds do not lead to neurodevelopmental impairment later in early childhood [47, 48]. However, evidence has emerged that suggests that neonates who received a blood transfusion within 48 h of surgery experience increased 30-day morbidity and mortality (OR 1.53) [49]. This report requires further clarification and validation to establish its veracity. In the meantime, either a liberal or restrictive transfusion protocol may be followed in neonates. A transfusion of 4 mL/kg of packed red cells increases the hematocrit by 4% and the hemoglobin by 1 gm/dL. The effect of such a transfusion will be clinically useful after 15 min and sustained for 24 h in the absence of further bleeding [50]. Neonates are susceptible to hypothermia, hypocalcemia, hyperkalemia, volume overload, and coagulation factor dilution after transfusion. "Newer" blood should be transfused (ideally fresh, irradiated, and washed pRBC within 6 h of washing) and it should always be warmed and administered with monitoring. When a massive transfusion (greater than half of the neonate's estimated blood volume) is required, the use of antifibrinolytics, clotting factors, and platelets should also be considered.

Platelets and Blood Products

Platelet concentrations decrease during neonatal sepsis or inflammation and are therefore often required perioperatively for emergency intestinal surgery. ABO group-compatible, Rh-identical, CMV-negative single donor platelets should be used where possible in a dose of 10–20 mL/kg. Fresh frozen plasma or equivalent products are used for DIC (disseminated intravascular coagulation) and vitamin K deficiency coagulopathy or during massive transfusion. This can be group AB or ABO compatible and is administered at a dose of 12–15 mL/kg. Cryoprecipitate is indicated if fibrinogen levels are <0.5 g/L preoperatively and should be maintained >1 g/L in the presence of bleeding [5].

Point of Care Testing

Access to blood sugar and blood gas monitoring is essential in all but the most straightforward neonatal surgery. Frequent blood sampling is a common cause of anemia in the neonate so it should be kept to a minimum and the dead space reinfused. Thromboelastography may be useful for guiding blood product administration in term neonates if appropriate reference ranges are available.

Minimally Invasive Surgery in Neonates

In some centers, laparoscopic surgery has become the standard of care for many abdominal and pelvic procedures in children of all ages including neonates. The benefits are well described and include quicker recovery times, reduced analgesia requirements, and a reduced stress response [51]. Perioperative anesthetic management can be challenging however, mainly due to the cardiorespiratory effects of a pneumoperitoneum, positioning, and sometimes inevitably longer procedure times. These issues are exacerbated in neonates.

Laparoscopic techniques have been described for:

- Inguinal hernia repair
- Pyloromyotomy
- Duodenal atresia repair
- Congenital diaphragmatic hernia repair
- Malrotation and Volvulus/Ladd's procedure
- Abdominal or ovarian cysts
- Anorectoplasty
- Pull-through procedures for Hirschsprung's disease

Physiological Effects of Laparoscopic Surgery

Insufflation of carbon dioxide to expand the intra-abdominal cavity can cause a number of physiological effects that are detrimental to the surgical neonate. Cardiovascular effects include vagally mediated bradycardia, reduced venous return, and increased systemic and pulmonary vascular resistance. These effects are exacerbated by extreme reverse Trendelenburg positioning or by the use of high insufflation rates and pressures and need to be appreciated in the presence of cardiac anomalies [52, 53]. Compared with older children, the neonatal peritoneum has a relatively large surface area and the abdominal wall is more pliable; therefore, surgical access can be achieved with lower abdominal pressures. It is recommended to use a slow rate of gas insufflation (<1 L/min) and a minimal IAP (intra-abdominal pressure) (6–8 cmH_2O) to minimize complications and to avoid or discontinue nitrous oxide as soon as possible after induction. Ensuring an empty stomach using a nasogastric tube facilitates surgical access and minimizes the need for a tense pneumoperitoneum.

Because the neonatal peritoneum is thin and relatively large and there is very little fat, clinically significant systemic absorption of carbon dioxide occurs, especially in surgeries of greater duration [54, 55]. Minute ventilation can be increased to offset the hypercapnia, but changes in lung compliance due to diaphragmatic splinting, small airway closure, and positioning can all affect ventilation. Use of a cuffed tracheal tube and hand ventilation can sometimes be useful. Where possible arterial carbon dioxide and acid-base status should be monitored during prolonged surgery and conversion to an open procedure should be an option if acidosis is profound or ventilation proves troublesome.

Transient oliguria may occur perioperatively due to IAP effects on renal blood flow and increased antidiuretic hormone levels. Fluid requirements are usually reduced compared with comparable open surgery. Bolus dosing of fluids should be avoided in response to reduced urine output unless the neonate is exhibiting additional signs of cardiovascular instability.

Although port incisions are very small (3 mm), postoperative pain can be significant if diaphragmatic irritation occurs. Good analgesia can usually be achieved with a combination of short-acting intraoperative opioids, paracetamol, and local anesthesia, either as surgical infiltration or using a regional technique such as caudal or transversus abdominis plane (TAP) block (see below).

Thoracoscopy has been steadily gaining popularity as the approach for congenital thoracic lesions [56–58]. A review and meta-analysis of published studies determined that thoracoscopic surgery is a reasonable alternative to thoracotomy in neonates [56, 59].

One-Lung Ventilation

Thoracic surgery ideally requires good access to the diseased lung and no risk of contamination of healthy lung. In older children, there are several options to achieve this; however, in neonates there is no appropriately sized specialist equipment (such as double-lumen tube or endobronchial blockers). The remaining options are endobronchial intubation using a conventional tracheal tube, or lung retraction by the surgeon. This is done either under direct vision or using gas insufflation via the thoracoscope [60, 61]. Use of a bronchoscope to facilitate an endobronchial intubation is difficult, since the smallest commercially available fiberoptic scope is 2.2 mm, has no suction channel, and requires a tracheal tube size of 3.5 mmID or greater to enable ventilation during the bronchoscopy. For this reason, the operative lung is often isolated by the surgeon and a conventional tracheal tube can be inserted into the trachea. This is a simple technique, but can result in inadequate lung collapse, soiling of the healthy lung, and no facility to suction or deliver CPAP to the operative side.

Postoperative Care

It may be possible for a term neonate undergoing simple surgery to go home on the same day after a suitable period of cardiorespiratory monitoring. Most neonates undergoing abdominal or thoracic surgery are required to stay overnight or a period of care in the NICU because of the risk of postoperative apnea in premature infants as well as term neonates [62]. Postoperative apnea is primarily an issue for infants less than 60 weeks post-conceptional age: the risk is greatest after general anesthesia and in the presence of anemia (Hb < 10 g/dL), a history of preoperative apneas, neurological conditions, or chronic lung disease as detailed below [62–64]. Balanced analgesia with local anesthesia and acetaminophen is suitable for shorter procedures. An opioid-based technique is suitable when prolonged monitoring or ventilation is planned. Detailed information on neonatal analgesia is covered elsewhere.

Specific Conditions

Congenital Thoracic Malformations

There are a number of congenital thoracic malformations that may require surgical intervention in the neonatal period. Congenital thoracic malformations may represent a spectrum of disease rather than discrete entities. The three commonest pathologies are congenital cystic adenomatoid malformation (CCAM), lung sequestration, and congenital lobar emphysema (CLE) [65].

Congenital Cystic Adenomatoid Malformation (CCAM)

This rare congenital lung lesion that occurs in 1:25–30,000 live births is the most common of the congenital thoracic malformations and the most common detected prenatally [66,

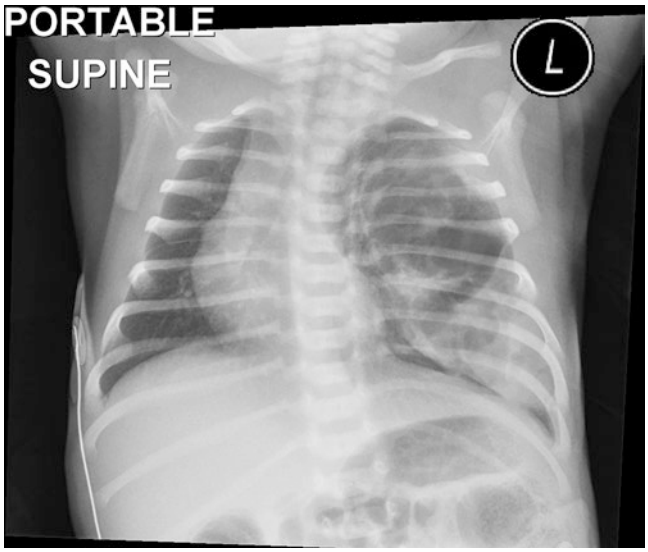

Fig. 9.1 Congenital cystic adenomatoid malformation. Chest radiograph in a neonate with a left-sided amorphous cystic mass filling most of the left hemithorax. The cardiac silhouette is shifted to the right. The right hemithorax is slightly opacified

67]. With advances in antenatal US and fetal MRI (accuracy 65–91%), we are detecting some lesions not identified previously and the true incidence may be greater. Congenital cystic adenomatoid malformation (CCAM) is a multicystic pulmonary mass usually affecting only one lobe of the lung, more commonly on the left, but may occur bilaterally in 5–15% (Fig. 9.1). The etiology is unknown, although it may represent a hamartomatous process, focal pulmonary dysplasia, or a bronchiolar developmental anomaly [68]. Identified growth factors (fGF-7) and genetic factors (Hoxb-5) have been implicated [67]. Anomalies associated with CCAM occur in up to 18% of cases, involving renal agenesis and cardiac defects (see type II below)[68]. The prognosis depends on the size of the CCAM and the cystic nature. Small lesions may be asymptomatic, but large lesions may be associated with hypoplasia of the normal lung and pulmonary hypertension and, in severe cases, mediastinal shift causing cardiac compromise and nonimmune fetal hydrops [69, 70]. Fetal hydrops is the most serious harbinger of death [71]. The ratio of the CCAM volume to the head circumference on the first antenatal ultrasound predicts the fetus' perinatal course: a ratio <0.56 is consistent with a good postnatal outcome, whereas a ratio >1.6 is consistent with developing hydrops [72].

Classification

Stocker originally classified CCAM based on cyst size and postnatal histology, yielding three types. Subsequently type 0 (tracheobronchial defect with small firm lungs and a bronchial airway) and type 4 (an entirely alveolar defect) were added to complete the current classification. Since types 1–3 are usually adenomatoid and types 1, 2, and 4 are cystic,

Table 9.1 The Stocker classification of congenital cystic adenomatoid malformation (CCAM)

Stocker type 0 (rare). This is a fatal defect in which the lungs do not develop beyond the pseudoglandular level, resulting in small hypoplastic lungs bilaterally with a bronchial airway. Also known as acinar dysplasia
Stocker type I (macrocystic adenomatoid malformation) (60–70%). Single or multiple large "cysts" (>2 cm diameter) are present, which communicate with the proximal airways and distal lung parenchyma. The lesion is relatively localized and most infants have a good prognosis after cyst resection. Good prognosis
Stocker type II (microcystic adenomatoid malformation) (10–15%). Multiple small spongelike cysts (<1 cm) replace the distal lung parenchyma. This has a worse prognosis and is more commonly associated with other anomalies, such as renal agenesis and cardiac and chromosomal abnormalities
Stocker type III (solid cystic adenomatoid malformation) (5%). The abnormality represents a severe end of the spectrum with multiple airless cysts involving an entire lobe or even lung. This has a poor prognosis, more commonly reported in stillbirths with CCAM
Stocker type IV (rare). This is an entirely alveolar pulmonary defect in which large cysts replace the numerous alveoli in the periphery of the lung. Good prognosis

Stocker proposed a broader term for these defects: congenital pulmonary airway malformations (CPAM) [66, 73]. However, CCAM remains the primary acronym for these defects. A simpler classification for this defect was proposed: macrocystic or microcystic (solid), based on anatomy and appearance on antenatal ultrasound, but Stocker's classification has persisted [66, 68, 72–74] (Table 9.1).

Diagnosis

The diagnosis is usually made by antenatal ultrasound at approximately 20 weeks' gestation [75–79]. The lesions are monitored throughout gestation following one of three courses: increase in size, remain unchanged, or undergo spontaneous resolution. In those with aggressive disease, the lesion may respond to maternal steroids. A few specialist centers offer fetal interventions for high-risk cases causing hydrops including thoracoamniotic shunt for isolated cysts, open fetal surgery, or an EXIT (ex utero intrapartum treatment) procedure at delivery (see Chap. 14), depending on gestational age, the size of the cyst, and the health of the mother [68, 77, 79]. Fetal MRI scanning is an excellent strategy to evaluate the volume of affected/unaffected lung and morphology of the lesion (T2 hyperdense lesion with cystic spaces).

Infants may present with symptoms of respiratory distress in the neonatal period, with tachypnea, increased work of breathing, and desaturation in 30% of cases, or occasionally with hyperinflation on the side of the CCAM. Some infants may be relatively asymptomatic. Ten percent of the neonates present with recurrent pneumonia or pneumothorax in later childhood. A significant number of neonates remain completely asymptomatic and are only detected incidentally.

CCAM may be evident on chest X-ray, especially if it is large. Microcystic lesions may be fluid filled, but macrocystic lesions are usually aerated and may be difficult to visualize. A CT scan with contrast is usually performed to delineate the limitations of the lesion. Ultrasound may be used to identify the blood supply and exclude an anomalous systemic artery. All cases identified antenatally require clinical and radiological investigation after birth even if asymptomatic to plan management.

Postnatal Management

Initial management involves respiratory support as needed and imaging to confirm and define the extent of the lesion. Neonates with hydrops have a very high perioperative mortality as a result of the pulmonary hypoplasia and pulmonary hypertension. These neonates should be medically stabilized before embarking on surgical interventions [70, 79]. Surgery may be beneficial for neonates with significant respiratory signs and symptoms and/or compression of adjacent cardiac or major vascular structures. Controversy exists regarding the appropriateness and timing of surgery in asymptomatic or smaller lesions [69, 80–83]. Resection in infancy or early childhood is increasingly advocated to preclude infectious complications and malignant transformation (rhabdomyosarcoma, squamous cell carcinoma, bronchoalveolar carcinoma, and pleuropulmonary blastoma in 2–4% of cases) and to encourage compensatory lung growth. Early surgery can also avoid the technical difficulties associated with resection after infection with less surgical complications [84]. If surgery is not undertaken, ideally these neonates should be followed into adulthood to ensure a timely intervention should the lesion turn malignant [83].

Surgical Considerations

The aim of surgery is to preserve viable lung tissue and reduce the mediastinal shift. The standard approach is posterolateral thoracotomy and lobectomy. Segmental resection may be used for small lesions or multilobular disease but is associated with a greater incidence of postoperative air leak. The margins of the lesion can also be difficult to assess and residual lesion may remain [67]. Thoracoscopic resection is increasingly being performed but access may be difficult with large cystic lesions [51, 57, 58, 85].

Lung Sequestration

This lesion consists of nonfunctioning lung tissue that does not have a tracheobronchial communication. There is anomalous systemic arterial supply, usually directly from the aorta, with more than one vessel in 15% of lesions. Sequestrations may have a patent or non-patent connection to the gastrointestinal tract (bronchopulmonary foregut malformations) [79].

Classification

- Intralobar sequestration (ILS) (75%): the abnormal tissue is contained within normal lung predominantly within the lower lobes (often left sided). The child is generally asymptomatic but may present with hemoptysis, pneumothorax, or recurrent infections in later childhood. The venous drainage is often via the pulmonary veins. Right-sided ILS may be associated with anomalous pulmonary venous drainage characteristic of scimitar syndrome; care must be taken to avoid ligating pulmonary veins during surgical resection.
- Extralobar sequestration (ELS) (25%): the sequestration is completely separated from the lung by visceral pleura. Arterial supply is infradiaphragmatic in 20% of cases and the lesion itself is infradiaphragmatic in 3%. Venous drainage is to the azygous system in the majority of cases. ELS affects males four times more commonly than females and is more often associated with other anomalies such as congenital diaphragmatic hernia (CDH) (16%), CCAM (15%), congenital heart disease, chest wall abnormalities, and hindgut duplications.

Diagnosis

These lesions may be detected on antenatal ultrasound or postnatal chest X-ray. The systemic blood supply must be delineated using ultrasound, CT, or MRI.

ELS is generally asymptomatic but is often detected earlier than intralobar sequestrations. Both ILS and ELS may be detected antenatally and may resolve. Symptomatic infants with large sequestrations may present with respiratory distress, feeding difficulties, or cardiac failure if the sequestered lobe is associated with significant arteriovenous or left-to-right shunting [79]. Hydrops may result from severe cardiac failure in utero, and pulmonary hypoplasia and pulmonary hypertension may be associated with large lesions, as in CCAM.

Management

Respiratory support should be instituted as required, and the systemic blood supply defined on imaging usually US or contrast-enhanced CT scan, as the first step. Surgical excision is generally advocated. The timing of surgery depends on the clinical situation. Complications such as infection and cardiovascular compromise due to shunting should be treated before resection.

Surgical Considerations

As for CCAM, thoracotomy is the standard approach for pulmonary sequestrations. Thoracoscopic resection is a viable alternative due to the relatively smaller size of the lesions. A laparotomy or laparoscopic approach is required for infradiaphragmatic lesions. Additional therapeutic interventions have been reported anecdotally including radiofrequency ablation and coil embolization [86].

The anomalous systemic vessels can be fragile elastic vessels with significant blood flow. Careful dissection and meticulous control are required to prevent hemorrhage. Control of the systemic blood supply during surgery is critical especially when the origin of the vessel is on the opposite aspect of the diaphragm to the operative field (infradiaphragmatic vessel for intrathoracic lesions). A loss of control can result in retraction of the vessel out of the operative field and catastrophic hemorrhage. A crossmatch should be available for all of these neonates.

Congenital Lobar Emphysema (CLE)

Congenital lobar emphysema (CLE) is a rare obstructive overinflation disorder, occurring in 1:20–30,000 live births with a sex predominance in males, 3:1 [87]. CLE may be due to defective bronchiolar development. The affected lobe is hyperinflated and may compress the adjacent normal lung. Hyperinflation becomes progressive after birth, although neonates usually present with respiratory distress in the first few days of life. The left upper lobe is involved in almost 50% of cases followed by the right middle lobe (28%) and the right upper lobe (20%); bilateral involvement is rare (Fig. 9.2). Cardiac anomalies are present in 20% of neonates with CLE [79, 87, 88].

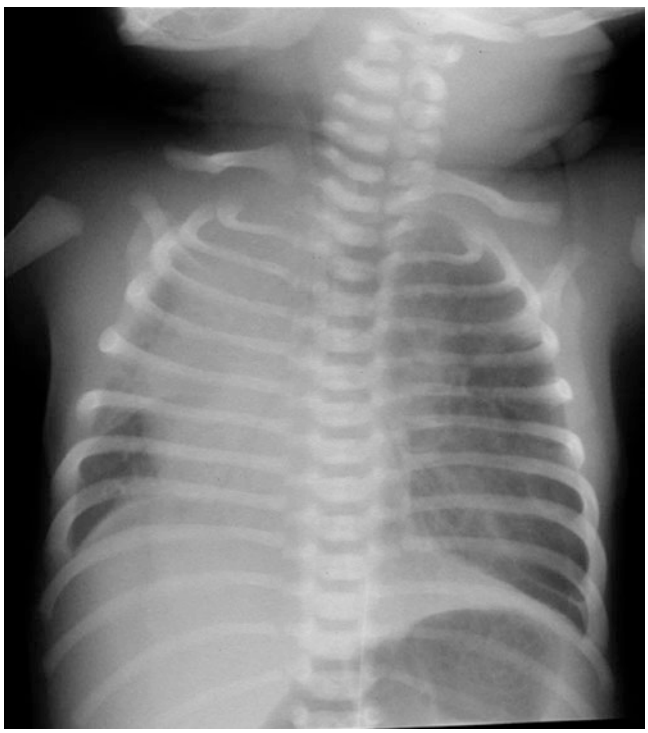

Fig. 9.2 Congenital lobar emphysema. Chest radiograph with hyperinflation of the left chest and displacement of the cardiac silhouette toward the right chest. A large gastric air bubble is present

Diagnosis

CLE may be detected antenatally but is difficult to distinguish from CCAM. Postnatally, there is often early respiratory distress and clinical signs suggestive of pneumothorax. A CXR may show lobar hyperinflation, mediastinal shift, and flattening of the ipsilateral diaphragm. Ultrasound can help distinguish from a tension pneumothorax, or if stable enough, CT or MRI scan will confirm the diagnosis. If the neonate is stable, then a preoperative echocardiogram should be also performed to identify congenital heart disease.

Management

The primary treatment is lobectomy, which may be required on an emergent basis before a full preoperative workup can be performed. More recently, segmental lung resection has proven successful in preserving lung without an increased incidence of a recurrence [89]. Positive pressure ventilation worsens the hyperinflation, and if respiratory support is required preoperatively, then HFOV may be preferred. A chest drain should never be inserted as it may cause preferential ventilation of the abnormal lung leading to respiratory failure [88].

Anesthetic Implications for the Management of Congenital Thoracic Malformations

Similar anesthetic principles and considerations exist for these lesions; hence, their discussion is appropriate. Thoracotomy and lung resection for CCAM are usually well tolerated. Full invasive monitoring is required but one-lung ventilation is usually not necessary. If the CCAM is connected to the bronchial tree, hyperinflation may lead to a ball-valve effect.

For infants have severe respiratory distress, HFOV (high-frequency oscillatory ventilation) may be required preoperatively, although the neonate is usually weaned to conventional ventilation early in the postop period [79]. Analgesia may be provided by intravenous opioids or thoracic epidural analgesia via a caudal catheter [90].

Similar management exists for cases of lung sequestration. Neonates with severe pulmonary hypertension should be medically managed before surgery. In general, pulmonary sequestrations do not become hyperinflated [91]. The anesthesiologist should however prepare for the risk of major hemorrhage as anomalous systemic blood vessel can have significant blood flow. These vessels can be challenging when the origin is on the opposite side to the operative field.

The airway may be secured with a tracheal tube after either an inhalational or IV induction with propofol. The blood or brain partial pressure of insoluble inhalational anesthetics such as sevoflurane is substantially reduced by right-to-left

shunts. Furthermore, end-tidal concentrations of sevoflurane do not reliably predict the brain partial pressure. Thus, end-tidal concentrations cannot be used to assess the depth of anesthesia with sevoflurane in neonates with these lung lesions. Depending on the surgical approach and recovery, the anesthetic prescription should either ensure reversible anesthesia for extubation after a thoracoscopic approach or a combination of an inhalational agent and opioids (fentanyl is preferred) to manage a thoracotomy and the chest wall pain that results.

In CLE surgery, all attempts should be focused to minimize excessive positive pressure before opening the chest. Positive pressure can result in rapid inflation of the emphysematous lobe and cardiovascular compromise. Spontaneous ventilation, manual assisted ventilation, and titrated pressure support are strategies that may be used to minimize peak airway pressures [92]. Nitrous oxide is replaced with air in these cases. Once the chest is opened however, ventilation should be controlled to ensure adequate oxygenation and ventilation.

Although technically challenging, lung isolation may be requested to protect the diseased lung from overinflation through endobronchial intubation or endoluminal insertion of a Fogarty catheter or bronchial blocker [61, 93]. Such devices are prone to dislocation due to the neonate's small size, surgical positioning, manipulation of the mediastinal structures, and compression of the diseased lung.

Patient-specific multidisciplinary case discussion can highlight concerns and a plan for emergency thoracotomy with surgeon/scrub team ready at induction of anesthesia.

Esophageal Atresia/Tracheoesophageal Fistula

Esophageal atresia (EA) and tracheoesophageal fistula (TEF) occur in 1:3000–1:4500 live births [94–96]. The etiology is believed to be due to a defect in the separation of the trachea and esophagus from a common foregut, which normally occurs after 4 weeks' gestation. The etiology and exact embryology remain unclear, although the theories put forth include failure of fusion of lateral tracheoesophageal folds or the tracheoesophageal septum, imbalance in epithelial proliferation and apoptosis, trifurcation of the lung bud, and a possible role of the notochord. Animal evidence suggests a greater developmental role of the foregut in this defect as the fistula and distal esophagus may be respiratory in origin [66]. There is also evidence that specific targets in the molecular mechanisms responsible for complete separation of the trachea and the esophagus may be responsible for EA/TEF defects [97].

Classification

First classified in 1929 (Vogt), and modified in 1953 (Gross), five common types of EA/TEF have been described, which are based on the anatomical variations seen. It is therefore most appropriate to describe the conditions anatomically [94, 95, 98] (Table 9.2; Fig. 9.3).

Table 9.2 EA/TEF classification and incidence in neonates

EA with distal TEF (80–85%)
Pure EA (5–7%)
Isolated TEF ("H"-type fistula) (3–6%)
EA with proximal and distal TEF (3–5%)
EA and proximal TEF (2%)

The length of the gap between proximal and distal esophagus is variable, as is the position of fistula (or fistulae) within the trachea (see Fig. 9.3). These anatomical variations have important implications for surgical strategy and anesthesia management. A long gap (type A or B or type C) where the fistula is at the carina makes a primary anastomosis far more difficult and different management approaches may be needed. In one series, the fistula was mid-tracheal in 61%, at or just above the carina in 33%, cervical in 8%, and bronchial in 1%. There was more than one fistula in 3% of patients [98, 99]. In the "H"-type TEF, the fistula is typically in the cervical region, whereas in EA with a proximal fistula, the fistula is usually 1–2 cm from the blind-ending upper pouch [96].

Neonates with EA/TEF are often born premature, with low birth weight (Fig. 9.4) [95]. Approximately 50% of neonates with EA/TEF have associated anomalies, an incidence that increases with decreasing birth weight (<2500 g) and with pure EA. In contrast, anomalies are less common in those with an isolated H-type fistula [95, 96, 100, 101]. The most common anomalies associated with EA/TEF are cardiac anomalies (29%), followed by duodenal atresia and anorectal anomalies (14%), genitourinary anomalies (14%), intestinal malrotation (13%), chromosomal abnormalities (trisomies 21, 18, and 13q deletion) (4%), vertebral and skeletal anomalies (10%), and specific-named associations (see below). The most common cardiac defects are atrial or ventricular septal defects or tetralogy of Fallot [101, 102] (Fig. 9.5) [103]. A right-sided aortic arch is present in 2.5–5% of infants with EA/TEF [104].

Several disorders have been associated with EA/TEF [95]. The VATER/VACTERL association, an association of unknown etiology, is defined by the presence of at least three of the following congenital malformations: *v*ertebral defects, *a*norectal anomaly, *c*ardiac defects, *T*EF, *r*enal anomalies, and *l*imb (radial) abnormalities [103, 105, 106]. Approximately 47% of neonates with EA have VACTERL anomalies.

VACTERL-H association is the VACTERL association with hydrocephalus, although hydrocephalus is often listed as a non-VACTERL anomaly (see above). CHARGE syn-

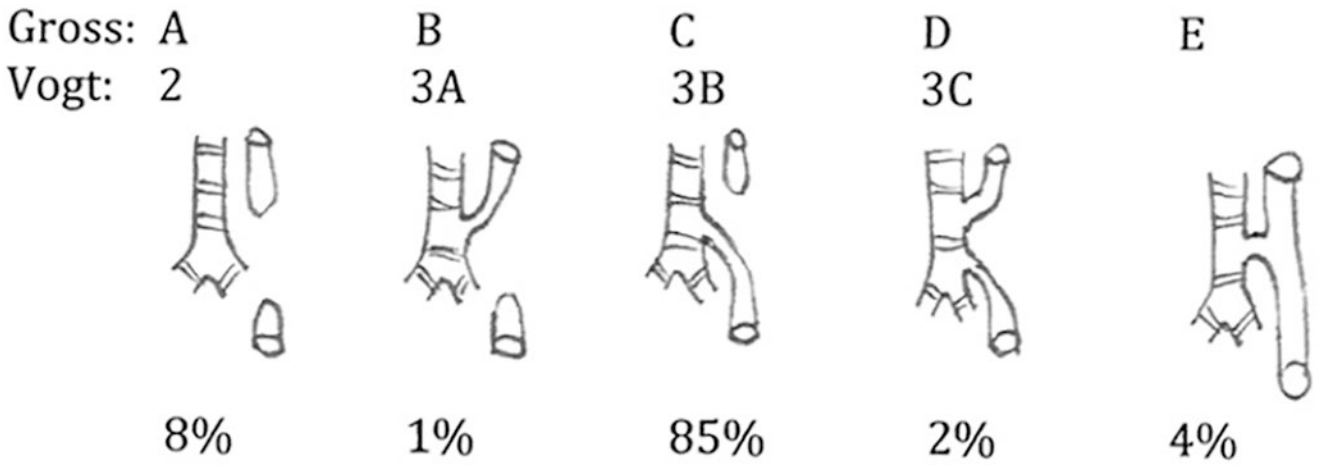

Fig. 9.3 Classification of trachea-esophageal fistula according to Gross and Vogt. The incidence of the variants is depicted under the drawing [95]

drome is an autosomal dominant disorder caused by a mutation on chromosome 7. It is associated with TEF, coloboma, cardiac defects, choanal atresia, neurocognitive and growth impairment, and genital, ear, and cranial nerve defects. Potter's syndrome, which is associated with renal agenesis, pulmonary hypoplasia, dysmorphic facies, and Schisis association, which is associated with omphalocele, cleft lip and/or palate, congenital diaphragmatic hernia, and neural tube defects, may also be associated with EA/TEF. EA/TEF is also associated with CATCH syndrome (22q deletion that includes cardiac defects, abnormal facies, thymic aplasia, cleft palate, and hypocalcemia). Of the trisomy syndromes, EA/TEF is most often associated with Edwards syndrome (trisomy 18). Feingold syndrome (dominant inheritance) is similar to VACTERL syndrome but features microcephaly and learning difficulties [95]. Other syndromes associated with EA/TEF include DiGeorge sequence, Pierre-Robin sequence, Fanconi syndrome, and polysplenia [66].

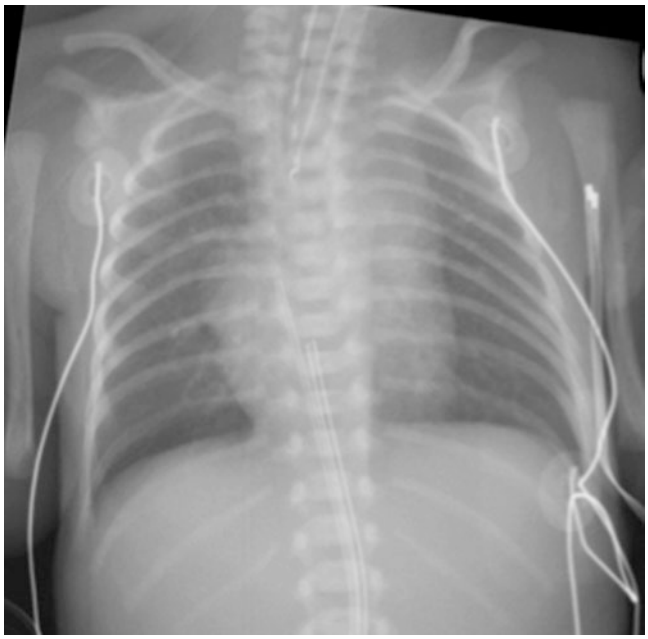

Fig. 9.4 Esophageal atresia in a neonate. This chest radiograph depicts a multi-orifice orogastric tube (with side holes) ending at the mid-thoracic level. A tracheal tube ends at the thoracic inlet. Umbilical vein and artery catheters enter radiograph from below; one terminates at T6–T7 and a second at T8–T9. A gastric air bubble is not visible here

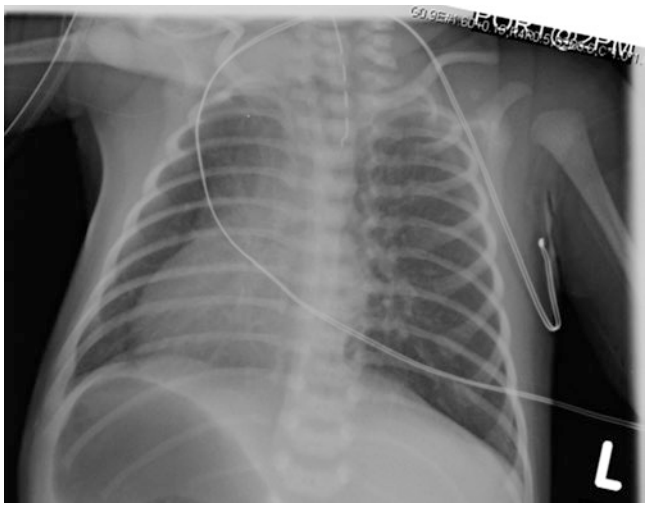

Fig. 9.5 EA/TEF with situs inversus. Chest radiograph of a neonate with EA/TEF. The multi-orifice orogastric tube (with side orifices) ends at T3–T4 reflecting EA. The cardiac silhouette and gastric bubble are reversed, present on the right side. Echocardiogram verified the presence of a ventricular septal defect. The large gastric air bubble is consistent with a distal tracheoesophageal fistula

Non-VACTERL anomalies are being reported in association with EA/TEF with increasing frequency. Such anomalies include single umbilical arteries, genital defects, digital defects, neurologic anomalies, and respiratory tract defects [103, 107].

Diagnosis

EA may be suspected antenatally in the presence of polyhydramnios with a small or absent gastric bubble or associated abnormalities present in the fetus. Most cases, however, present after birth. A history of polyhydramnios should prompt the pediatrician to pass a size 8–10 Fr orogastric tube immediately after birth. With EA, the tube cannot pass the upper esophagus and will coil in the upper chest on XR. The diagnosis is strongly suspected clinically in the first few hours after birth if mucous that accumulates in the upper airway cannot be cleared by swallowing and an orogastric tube cannot be passed. The neonate chokes or becomes cyanosed if it attempts to feed. Aspiration pneumonia due to delayed diagnosis was common decades ago but should now be uncommon with good clinical awareness.

The diagnosis of EA/TEF should be confirmed on plain X-ray of the chest and abdomen. A coiled nasogastric tube will be identified in the upper third of the esophagus (level T2–T4); air in the gastrointestinal tract indicates the presence of a distal TE fistula. A gasless gastrointestinal tract suggests the absence of a distal fistula, although a proximal fistula remains a possibility. Other abnormalities such as vertebral anomalies (usually in the lower thoracic region) or the "double bubble" of duodenal atresia can also be detected on preoperative films. A thorough clinical examination is important to exclude associated anomalies and the presence of coexisting problems, such as respiratory distress syndrome in premature infants. An echocardiogram is strongly recommended before surgery to identify cardiac defects and the position of the aortic arch. If the neonate has passed urine (thus excluding bilateral renal agenesis), then a renal ultrasound can be delayed until after surgery.

An H-type TEF is infrequently detected in the neonatal period but should be suspected with a history of recurrent chest infection due to repeated aspiration.

Risk Stratification

It is helpful to stratify neonates with EA/TEF according to risk. The original stratification by Waterson was based on birth weight, associated anomalies, and the presence of pneumonia [96]. Neonatal care has improved leading to a current risk stratification that is based solely on birth weight and the presence of cardiac anomalies [101, 102, 108]. Improved outcomes have resulted in survival rates exceeding 98% in neonates with birth weights >1500 g and without major cardiac anomalies, 82% with birth weights <1500 g or major cardiac anomalies, and 50% with birth weights <1500 g and major cardiac anomalies [108]. A four-part classification has been suggested more recently, with prediction of 100% survival in neonates with birth weights >2000 g without cardiac anomalies and 40% survival in high-risk neonates with birth weights <2000 g with major cardiac

anomalies [102]. The premature infant with a major cardiac anomaly remains a high risk. Parents of infants with significant chromosomal anomalies (trisomy 18), unrepairable cardiac defects, bilateral renal agenesis, or other major complications of prematurity with very poor prognosis may be given the option of nonoperative treatment**.**

Medical Management

Initial management of neonates with EA/TEF is to prevent aspiration of oral secretions before definitive surgery. A 10 Fr double-lumen oro-esophageal Replogle tube should be inserted into the upper pouch and placed on continuous suction, or secretions should be cleared frequently by naso-esophageal tube suction. The neonate should be given maintenance intravenous fluids and nursed 30° head up or in the decubitus position. Blood should be crossmatched and available for surgery. If preoperative ventilation is required, inspiratory pressures should be kept to a minimum, if possible placing the tip of the tracheal tube distal to the fistula (see below). Premature infants should receive surfactant according to standard protocols.

Surgical Considerations

The aim of surgery is to restore continuity of the esophagus and ligate the TE fistula, if present. Surgery is usually performed on the first or second day of life if the neonate is stable and does not require respiratory support. The operation should ideally be scheduled during daylight hours given the complexity of both the surgery and anesthesia. Primary esophageal anastomosis is usually possible in EA with distal TEF unless a very wide gap is found with a low carina fistula. In a neonate with severe comorbidities such as a duct-dependent cardiac anomaly or extreme prematurity, it may be preferable to divide the fistula and place a feeding gastrostomy. Delayed primary esophageal repair can be performed 6–12 weeks after cardiac surgery or when the baby is more robust. This may also be possible if a wide gap is found.

Emergency surgery may be required if the child requires preoperative ventilation, as in the case of the preterm neonate with respiratory distress syndrome. If the lung compliance is poor, gas from the ventilator may preferentially enter the gastrointestinal tract via the fistula. This may lead to gastric distension, deteriorating cardiorespiratory status, and possible gastric rupture. Inadvertent intubation of the fistula must be excluded in cases of severe gastric distention with cardiorespiratory instability [109]. To prevent gastric distention from ventilation via the fistula, some have recommended clamping the distal esophagus as soon as the chest is opened [110]. Decompressive gastrostomy should not be undertaken as a primary intervention as it will lead to a torrential gas leak via the gastrostomy and worsening minute ventilation. The child should undergo emergency transpleural ligation of the fistula, with consideration of delayed division of the fistula and possible repair of EA within 8–10 days [96].

Neonates with pure EA or EA with a proximal TEF often have a long gap between proximal and distal ends of the esophagus. A feeding gastrostomy is made via laparotomy which can be technically challenging as the stomach is usually very small. The length of the gap should be estimated radiographically at the time of surgery with a probe or urethral sound from the stomach and the Replogle tube in the proximal pouch both under gentle tension. If the gap is greater than the vertical height of three vertebral bodies, upper pouch suction is continued postoperatively and delayed primary closure is usually possible by about 12 weeks of age; if the gap is greater than six vertebral bodies, a cervical esophagostomy is often fashioned and the esophagus repaired at a later date. Esophageal replacement surgery is often required in this situation although esophageal lengthening procedures both open and thoracoscopically have been reported with varying success [96, 111].

An esophagoscopy or bronchoscopy should be performed at the start of surgery to provide absolute confirmation of the diagnosis, to assess the position of the fistula if present, and to exclude multiple fistulae [98, 99, 112, 113]. A variety of techniques have been described to identify fistulae in neonates: rigid bronchoscopy, esophagoscopy, or flexible fiberoptic bronchoscopy via the tracheal tube. The advantage of using a small flexible bronchoscope is that the scope may also be used to assess the position of the tip of tracheal tube, to pass through the fistula to assist the surgeon in identifying the fistula during surgery, and to assess the airway at the end of surgery to exclude a residual blind-ending tracheal pouch and the severity of the tracheomalacia near the fistula [114].

The traditional approach to repair of EA/TEF is extrapleural via a right posterolateral thoracotomy with the neonate placed in the lateral decubitus position with a roll under the chest to facilitate surgical access. The posterior mediastinum is approached via the 4th and 5th intercostal spaces with extrapleural dissection gently compressing the right lung. The approach is delicate and time-consuming but potentially reduces morbidity from an anastomotic leak, should one occur. If a right arch is confirmed on preoperative echo, a left-sided approach should be considered although repair is certainly still possible from the right and a double aortic arch may be approached via the standard right thoracotomy [104]. If the child becomes unstable, a transpleural approach may be used.

Thoracoscopic repair has become popular in specialist centers in recent years and, in expert hands, has the same surgical complication rate as open techniques, with comparable blood gases and operating times, but with reduced time in intensive care postoperatively and length of stay [59, 114–120]. Currently recommendations are based on large case series, since no randomized controlled trials have compared the two techniques [117, 118, 121]. For thoracoscopic repair, the child is placed semiprone with the right side of the chest

elevated at 45° so that the structures may be easily visualized. Lung deflation is produced by CO_2 insufflation, and care should be taken to minimize hypercarbia, as described previously.

Major concerns during open or thoracoscopic surgery include accurate identification of anatomical structures and cardiorespiratory instability due to OLV and distortion of the trachea. The anesthesiologist may be asked to push on the Replogle tube to help identify the proximal esophageal pouch. Test occlusion of the fistula is good practice to ensure that the right lung can still be inflated and that a vital structure (e.g., the pulmonary artery or a main bronchus) has not been clamped in error. If the neonate does not tolerate OLV, surgery may have to proceed with intermittent two-lung ventilation once the neonate recovers. This requires good communication between the anesthesiologist and surgeon. Increased FiO_2 and hand ventilation may be required, but respiratory compromise usually improves after ligation of the fistula. The integrity of tracheal repair can be checked by instilling warm saline in the chest during a sustained inflation to identify an air leak by the presence of air bubbles. The lower esophagus should not be aggressively mobilized in order to avoid devascularization, as this may cause later problems with esophageal motility. A gas leak from the upper pouch during esophageal anastomosis should raise suspicion of an upper pouch fistula. Dissection of the upper pouch helps to identify a proximal fistula, if one is present, and allows mobilization of the esophagus to minimize tension of the repair. If there is significant tension at the anastomosis, the neonate should remain paralyzed and the lungs ventilated mechanically for approximately 5 days postoperatively [96]. A transanastomotic tube (TAT tube) placed under direct vision before the anastomosis is completed facilitates early feeding in the absence of a gastrostomy and should be clearly marked to preclude accidental removal postoperatively.

Early complications at EA/TEF repair include tracheobronchomalacia (20–40%), anastomotic leak (15–20%), anastomotic stricture (30–50%), and recurrent fistula (10%) [122]. Tracheomalacia is due to abnormal cartilage in the region of the fistula and often produces a typical barking cough. In severe cases, the child may develop recurrent chest infections or "near death" episodes due to acute airway collapse, and emergency aortopexy may be required in the first few months after repair [96]. An early anastomotic leak may cause a tension pneumothorax; a chest drain should be inserted and the leak explored and repaired. Late complications include gastroesophageal reflux (severe reflux in 40%) and recurrent chest infections, probably related to gastroesophageal reflux [95]. Long-term respiratory complications including bronchiectasis may result from aspiration, GERD, and chest wall abnormalities [123]. Both the parents and their neonate are at risk for psychological and traumatic stress (including post-traumatic stress disorder) [124]. These are long-term issues centered around feeding difficulties, multiple painful procedures and surgeries, feeding, and airway issues.

Anesthetic Considerations

General anesthetic issues include principles in the neonate with a high incidence of comorbidity and those specific to thoracotomy or thoracoscopic procedure. Anesthetic challenges for these cases include facilitating accurate identification of the anatomical structures, cardiovascular instability due to anesthesia, one-lung ventilation, and the effect of surgical manipulation of structures.

Selective OLV is not necessary as the surgeon can compress the neonatal lung to access the fistula. The anesthesiologist may be asked to push on the Replogle tube or advance an appropriately sized tracheal tube to help identify the proximal esophageal pouch.

There has been evolution in the role of thoracoscopic repair of TOF /OA repair. Concerns have been highlighted over the cardiovascular effects of prolonged thoracoscopic surgery, the need for high airway pressures resulting in hypoxia and hypercarbia, and its effect on the newborn central nervous system. Recent reviews from centers experienced in this minimally invasive technique suggest similar results but an increased incidence of stricture or anastomotic breakdown in the thoracoscopic cohort [120].

Preoperative ECHO is mandatory to identify the presence of congenital heart disease ranging from PDA or ASD/VSD morphology to hypoplastic left heart syndrome. Failure to correctly identify congenital cardiac lesions can result in catastrophic complications including hypoxia, hypotension, and irreversible cardiac arrest.

Airway management and positioning of the tracheal tube in the presence of a fistula is extremely challenging. Anesthetic challenges include intubation of the fistula leading to gastric distension and splinting of the diaphragm and difficult ventilation [108, 125, 126]. The majority of complications occur with a large fistula occurring at the level of the carina.

A variety of anesthetic techniques and airway management strategies have been described [96, 114, 125–128]. Most advocate inhalational or intravenous introduction according to personal preference, with muscle relaxant and gentle ventilation before intubating the trachea [114, 125–128].

One technique popularized was to deliberately intubate the right main bronchus, rotate the tube to position the bevel towards the sternum, and then withdraw the tube until bilateral air entry is confirmed. This ensures the tube is below the fistula but does not prevent intubation of a large carinal fistula [109].

A collaborative approach with ENT colleagues would enable a diagnostic MLB to delineate the anatomy of the airway,

exclude laryngeal cleft, and facilitate positioning of the endotracheal tube relative to the fistula. The distance between the fistula and the glottis and carina, respectively, may be measured using rigid bronchoscopy [128]. This is facilitated with spontaneous ventilation and lidocaine topically applied to the larynx. Spontaneous ventilation is maintained until the fistula is ligated; after that, neuromuscular blockade can be safely administered.

If the fistula is mid-tracheal, the tip of the tracheal tube is ideally positioned just below the fistula with bevel facing anteriorly as the fistula originates from the posterior wall with gentle positive pressure ventilation. Provided the fistula is small at the carina, the tracheal tube can be positioned mid tracheal. It is imperative that the tracheal tube is fixed carefully and checked after positioning to ensure the dependent lung remains ventilated.

In the unusual situation of a large fistula at the level of the carina resulting in preferential gastric ventilation, some authors suggest passing a 2/3 Fr Fogarty embolectomy catheter through the fistula into the stomach via a rigid bronchoscope and occluding the fistula through inflation of the balloon. The tracheal tube is positioned alongside the Fogarty catheter. This may not be possible so a surgeon should proceed to thoracotomy to ligate the fistula as quickly as possible. An alternative strategy may be thoracotomy and ligation of distal esophagus below the fistula. If the stomach becomes very distended before the fistula is ligated, the tracheal tube can be intermittently disconnected to decompress stomach via airway.

Analgesia may be managed using an opioid-based technique such as fentanyl or remifentanil intraoperatively and intravenous morphine postoperatively particularly for the child with long-gap EA who will remain ventilated postoperatively. Caudal catheters have been described and are most suitable for low-risk infants who are candidates for early extubation immediately postoperatively. Many pediatric surgeons prefer a controlled extubation by the anesthetic team immediately postoperatively to reduce the need/risk for emergency reintubation that may damage surgical closure or to leave the tube in place for several days to ensure adequate postoperative analgesia can be provided without the risk of respiratory distress and emergency reintubation.

Blood loss is usually minimal; intravenous crystalloid such as Hartmann's solution is ideal and a fluid volume of 10–20 mL/kg is usually required. Blood glucose monitoring is essential. Broad-spectrum antibiotics should be administered before skin incision and continued as per the surgical discretion.

Secure intravenous access should be established and many anesthesiologists advocate for arterial access to facilitate beat to beat monitoring and arterial blood gas sampling during one-lung ventilation, although this is not necessary. Cranial NIRS (near-infrared spectroscopy) may have a role in the continuous intraoperative monitoring as suggested from the critical care environment although no studies have been forthcoming [129].

Neonates with cardiac disease have a greater incidence for critical events such as desaturation and need for new inotropic support compared with those without cardiac disease as well as a 57% mortality during hospitalization for those with ductal-dependent congenital heart disease [100]. These data underscore the need for preoperative ECHO and if a heart defect is present to discuss the need for central venous access. Phenylephrine should be prepared to treat a "tet spell" in a neonate with an unrepaired tetralogy of Fallot.

Congenital Diaphragmatic Hernia

Congenital diaphragmatic hernia (CDH) occurs in 1:2,500 live births, with a slight predilection for males. There are two major types: Bochdalek (posterolateral defect) (Fig. 9.6a, b) and Morgagni (anterior) (Fig. 9.7a, b) [130]. The posterolateral defect accounts for 85–95% of cases of CDH and most are diagnosed antenatally. CDH is associated with herniation of the abdominal viscera into the affected hemithorax, with displacement of the mediastinum to the contralateral side (Fig. 9.6a, b). The lung on the side of the hernia is hypoplastic, whereas the lung on the contralateral side is usually normal (if survival is likely) or hypoplastic (if survival is unlikely). The degree of lung hypoplasia and associated pulmonary hypertension are the major determinants of outcome; surgical repair of the diaphragm has a relatively minor contribution to the long-term outcome. Anomalies occur in 40–60% of neonates with CDH. These include cardiac, neural tube, chromosomal, renal, and genital anomalies and pulmonary sequestrations, as well as malrotation and duodenal atresia [131, 132]. The anterior (Morgagni) defect accounts for only 2% of diaphragmatic hernias, located retrosternal (at the level of the xiphoid) or anteromedially in the diaphragm (Fig. 9.7a, b). These are often asymptomatic and may not be detected until adulthood or found incidentally with other investigations such as CT scanning for cardiac anomalies [133].

Embryology

The diaphragm develops during weeks 4–8 from four embryological elements. A Bochdalek hernia results from failure of closure of the pleuroperitoneal canals during early embryonal life, often with early in-growth of the liver through the defect. The exact cause for CDH remains unknown but may be associated with genetic factors that lead to failure in cell migration, myogenesis and formation of connective tissue, or abnormalities of the retinoid signaling pathway, which is important in the development of the diaphragm. CDH may occur as an isolated abnormality (often associated with a mutation on chromosome 15q26) or occasionally associated with syndromes such as Pallister-Killian, Fryns syndrome, Cornelia De Lange, or Edwards syndrome [131]. Abnormal

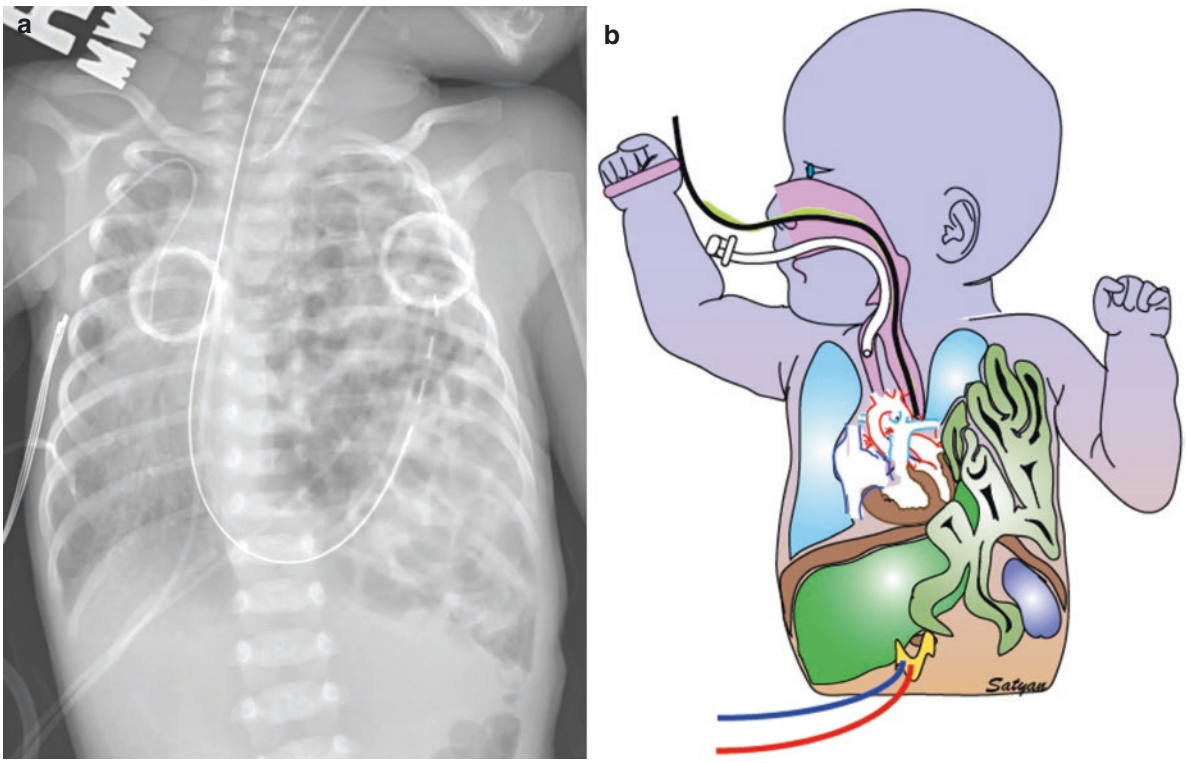

Fig. 9.6 Congenital diaphragmatic hernia (CDH): foramen of Bochdalek defect. (**a**) This chest radiograph depicts a neonate with congenital diaphragmatic hernia in the left (classic Bochdalek defect) chest with stomach and bowel in the chest, displacing the heart to the right chest. Note the multi-orifice orogastric tube (with side holes) in the esophagus, curving up and across the diaphragm and terminating in the stomach in the left chest. The tracheal tube ends at the thoracic inlet. PICC line enters the right chest and ends in the superior vena cava. (**b**) A schematic of a neonate with a CDH with bowel present in the left chest; the right lung is compressed and the heart is deviated toward the right chest (Courtesy of Dr. Satyan Lakshminrusimha, Division of Neonatology, Women and Children's Hospital of Buffalo, Buffalo, NY)

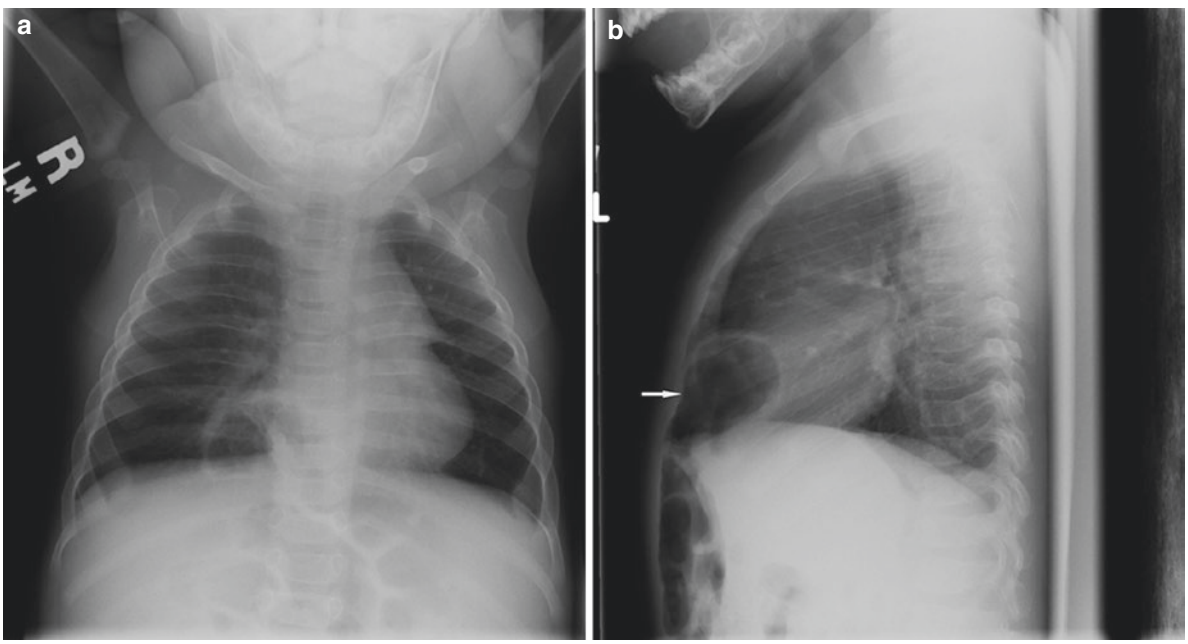

Fig. 9.7 (**a**, **b**) Congenital diaphragmatic hernia. Foramen of Morgagni defect. (**a**) This AP chest radiograph depicts a neonate with congenital diaphragmatic hernia with a loop of bowel that herniated through a defect in the anteromedial (retrosternal) area of the diaphragm (foramen of Morgagni). (**b**) This lateral chest radiograph depicts a loop of bowel in the immediate retrosternal space (see *arrow*), rising above the anterior aspect of the diaphragm (Courtesy of Dr. K. Valle, Division of Pediatric Surgery, Women and Children's Hospital of Buffalo, Buffalo, NY)

karyotyping has been reported in 16% of neonates with CDH, in 4% of those without anomalies, and 39% of those with anomalies [134, 135].

Diagnosis

The diagnosis of CDH is made by antenatal ultrasound in ~70% of cases, due to the presence of intrathoracic bowel loops or stomach, often signaled by a history of maternal polyhydramnios [133, 136]. All cases should be referred to a specialist center. The fetus should be screened for associated anomalies and the family provided with antenatal counseling, particularly if there are features associated with a poor prognosis (see below) [137, 138]. Antenatal MRI scans may provide further prognostic information about lung volume, liver herniation, left ventricular mass, and pulmonary diameter and is becoming more commonplace but not routine [131, 139].

Postnatally, the neonate may present with an exacerbation of their respiratory distress. Symptoms may range from mild to severe, depending on the severity of the CDH. The abdomen is scaphoid as the intestine is in the chest, and breath sounds are reduced on the affected side. The diagnosis is confirmed by X-ray of both the chest and abdomen, which helps differentiate from other chest pathologies such as CCAM. A nasogastric tube should be placed before imaging as this may lie or curl above the diaphragm if the stomach is in the chest. An echocardiogram should be sought to delineate associated cardiac abnormalities and to estimate the severity of pulmonary hypertension [140]. Serial cranial ultrasound should be performed to exclude an intracranial bleed.

Outcomes

Despite the advances in the medical and surgical management of this condition, the overall mortality remains at 21–48%. However, specialist centers with a large number of cases have better survival rates of up to 80% live births [141]. Mortality in non-syndromic infants is primarily related to pulmonary hypoplasia and pulmonary hypertension and, as surrogate markers of severity, the need for ECMO/HFOV or for patch repair [142]. Right-sided, bilateral, or large defects, a lung to head ratio of 1.0 or less, and the presence of the liver in the chest portend worse outcomes, as do prematurity, chromosomal anomalies, severe cardiac defects (particularly transposition of the great arteries or single-ventricle physiology), and spinal anomalies [143, 144]. In an effort to establish a standardized scoring system, an international consensus concluded that the size of the diaphragmatic defect (as a surrogate for the severity of pulmonary hypoplasia and hypertension) and the severity of the cardiac defect may predict outcome [145]. ECMO required for more than 2 weeks or associated with renal complications or persistent pulmonary hypertension for more than 3 weeks is also associated with high mortality [137, 138, 141, 142].

Morbidity associated with CDH in the longer term includes ongoing respiratory problems with recurrent infections and reduced exercise capacity compared with age-matched peers, neurocognitive defects secondary to neonatal hypoxia or intracranial hemorrhage, and visual impairment and deafness, possibly related to intensive care management. Gastroesophageal reflux is common and may require medical or surgical intervention. Recurrence rates of up to 50% are reported in CDH especially if the initial defect is very large. Scoliosis and chest wall deformity may also occur [131, 146, 147].

Antenatal Treatment

Antenatal treatment for CHD has been trialed with varying success. The most promising treatment is fetal endoscopic tracheal occlusion (FETO) with a balloon for those with poor prognosis based on lung measurements. FETO prevents the egress of lung fluid from the fetal lung and improves lung growth and reduces vascular resistance. The tracheal balloon is either removed before delivery, by EXIT, or punctured immediately after delivery by tracheoscopy or percutaneous puncture ǂ[148, 149]. Promising results have been reported, although the complication rate is relatively great and may include previously unrecognized conditions such as tracheomegaly or bronchomegaly and remains under review [150, 151]. Premature delivery contributes to the poor outcomes of FETO [148]. In a randomized controlled trial of FETO, survival improved in neonates with isolated severe CDH [148, 149, 152].

Medical Management

Medical management of CDH has changed dramatically over the last two decades, from a strategy of early emergency surgery with aggressive hyperventilation to reduce pulmonary hypertension to optimizing the cardiorespiratory status using a "gentle ventilation" strategy to minimize barotrauma that includes minimum peak inspiratory pressures, maintaining spontaneous ventilation and permissive hypercarbia followed by a planned, surgical intervention [153, 154].

Delivery should be planned at or near a center with pediatric surgical and NICU expertise so that the optimal postnatal respiratory support and timely surgical intervention can be provided. The neonate should be allowed to mature to term to permit maximum maturation of the lung. A nasogastric tube should be passed after delivery to decompress the stomach, central and arterial access obtained, and the warming strategies commence with minimal handling. Pulmonary surfactant has not been shown to be beneficial [155].

The perinatal management of patients at delivery to optimize outcomes is attracting increasing attention [156]. Interventions such as early intubation and ventilation require further review as ideal practice is not clear. Initial ventilation strategy (conventional or high-frequency oscillation) varies among centers. The only randomized trial between conventional and high-frequency oscillation, the VICI-trial, found

no difference in mortality at 1 year of age or the frequency of bronchopulmonary dysplasia [157]. However, that study was terminated prematurely due to fiscal reasons resulting in a power of only 44%. Hence, we cannot infer from these results that the two modes of ventilation have equipoise. Optimal ventilation should aim for a pre-ductal SpO_2 85–95%, post-ductal SpO_2 >70%, arterial pCO_2 45–60 mmHg, and pH >7.25. If a conventional ventilation strategy is used, the initial settings should include a peak inspiratory pressure (PIP) 20–25 cmH_2O, positive end-expiratory pressure (PEEP) 2–5 cmH_2O, and a frequency 40–60 breaths per minute with minimum required inspired oxygen to maintain the threshold oxygen saturation [157, 158]. Prolonged use of muscle relaxants is ideally avoided, and the neonate should be allowed to breathe spontaneously between assisted breaths. If HFOV is used, the initial settings should include a mean airway pressure 13–17 cmH_2O, frequency 10 Hz, amplitude (ΔP) 30–50 cmH_2O, and I/E ratio 1:1 [157, 158]. Hyperinflation of the lungs should be avoided (<8 ribs on unaffected side on chest X-ray).

Echocardiography should be performed to estimate the pulmonary artery pressure, direction of shunting across the arterial duct/foramen ovale, myocardial contractility, the presence of a congenital heart/vascular defect, and the response to treatment. The oxygenation index (OI) should be calculated (OI = mean airway pressure (cmH_2O) × FiO_2 × 100/PaO_2 (mmHg)). iNO 10–20 ppm may be indicated if the OI is >20 or the pre-/post-ductal oxygen saturation difference is >10%. The use of iNO is controversial and response should be assessed using echocardiography. Prostacyclin or prostaglandin E1 (PGE1) should be considered if there is no response to iNO. Many units use PGE1 routinely to prevent closure of the arterial duct and to off-load the right ventricle. Sildenafil or milrinone may be indicated if pulmonary hypertension is refractory to treatment or persistent, but may cause systemic hypotension [159]. The early use of sildenafil in the management of pulmonary hypertension has also been proposed and there is currently a trial underway comparing this to iNO [160].

Endothelin receptor antagonists (bosentan) and tyrosine kinase inhibitors (imatinib) are currently under investigation. Fluid boluses may be required if peripheral perfusion is poor or hypotension is present. If cardiovascular instability persists, inotropes may be required to increase the mean arterial pressure to the upper normal range in order to reduce right-to-left shunting across the arterial duct.

Venoarterial extracorporeal membrane oxygenation (ECMO) may be offered in some centers as temporary stabilization and support in cases of severe cardiorespiratory failure [161]. Specific ECMO criteria vary between centers; current European criteria for ECMO include inability to maintain pre-ductal saturation >85% or post-ductal saturation >70%, respiratory or metabolic acidosis with a pH <7.15, need for aggressive ventilation, or refractory systemic hypotension [162]. The neonate should be >2 kg and >35 weeks' gestation, have no lethal congenital abnormalities, have no irreversible organ dysfunction (including neurological injury), and have no contraindication to systemic anticoagulation.

Surgical Considerations

The objectives of surgery in the management of CDH are to reduce the herniated contents safely into the abdomen and repair the defect. Ideally, surgery should be delayed until the neonate is stable, that is, off inotropes (with the possible exception of dopamine) for 24 h. Some have used "stability" criteria to determine the neonate's eligibility for surgery; however, these criteria may be more appropriate for determining the timing, rather than eligibility, for surgery [163]. Surgical intervention is possible while the neonate is on ECMO, although studies suggest that the mortality was increased because of a greater risk of bleeding [164]. Many centers undertake surgery only after weaning the neonate from ECMO and decannulation with possible improved survival [164], although some have achieved improved mortality rates repairing CDH on ECMO by limiting the use of anticoagulants and using antifibrinolytics [163, 165]. For large defects, a patch repair may be required which should be fashioned as a dome shape rather than a flat repair. This extra patch allows widening of the thoracic diameter with growth without the patch detaching and ideally minimizes the risk of recurrence [166]. Surgery may be performed by using an open technique (usually laparotomy) or increasing a minimally invasive technique [167].

Laparotomy via an upper abdominal transverse incision allows good access to the length of the diaphragm and can be extended easily if further access is required. The abdominal contents are reduced into the abdomen and the defect is identified. The spleen may require gentle finger reduction rather than simple traction on the gastric and colonic attachments, to avoid damage and bleeding. A hernial sac, which is present in 10–20% of cases, is usually excised during surgery. Pulmonary sequestrations may also be found, either supra- or subdiaphragmatic, and these are also excised. The hypoplastic ipsilateral lung may be seen via the defect in the chest. The diaphragmatic rim should be mobilized and, if possible, a primary repair performed without tension using nonabsorbable interrupted sutures. If the diaphragm is deficient laterally, then the sutures should incorporate a large bite of rib or muscle to prevent recurrence. If the defect cannot be closed without tension or is very large, a patch repair is required, although this technique is associated with worse short-term and long-term outcomes. A variety of nonabsorbable materials have been used, including Gore-Tex®, Marlex®, Dacron®, and Silastic®. Nonabsorbable materials have the advantage of cost, reduced bleeding, and easy handling; however, they do not grow with the child and may actually shrink over time. These materials are associated

with adhesions, increased recurrence, gastroesophageal reflux, and chest wall deformities [168]. Newer biosynthetic patch materials such as collagen lattices with embedded growth factors (Surgisis®, AlloDerm®) are under investigation, although they may increase the risk of postoperative small bowel obstruction and have higher longer-term failure and recurrence rates especially in large defects. Techniques that involve muscular flaps have been described, but they are time-consuming and may be associated with increased bleeding and abdominal wall deformity. Myogenic patches may be developed in the future [168]. A chest drain is not used routinely as the underwater drain may cause overdistension of the hypoplastic lung. Such a drain may be inserted at a later date if a clinically significant effusion develops. The advantage of the abdominal approach is that a Ladd's procedure can be performed at the same time if the position of the duodenojejunal (D-J) flexure is consistent with malrotation and there is the potential for volvulus.

MIS for CDH has been reported using both laparoscopic and thoracoscopic approaches. The laparoscopic approach enables better instrument handling for the diaphragmatic repair. Reduction of contents against the pneumoperitoneum and the subsequent lack of intra-abdominal space after reduction can be challenging. The thoracoscopic approach is preferred by many and has the advantage that the pneumothorax encourages lung reduction and there is an excellent view of the diaphragm after reduction. The lateral suture placement can be very difficult due to the rigidity and shape of the thoracic cavity. Initial reports of thoracoscopic repair also suggested an early greater recurrence rate; however, recovery and other surgical complications such as adhesive bowel obstruction may be improved [169–171]. Right-sided CDH, CDH-associated liver herniation, and the need for patch closure may be better suited for an open procedure. As for thoracoscopic repair, carbon dioxide absorption and acidosis can be problematic during MIS although the effect of this can be minimized with lower IAPs [55, 118, 172]. For this reason, an open surgical approach may currently be preferred for neonates with CDH and congenital heart disease, for those who required ECMO, or for those who have continuing systemic right ventricular pressures or require significant inotropic support [173].

It is important to avoid a "flat" diaphragmatic repair during primary or patch repair. When the herniated chest contents are reduced into the abdomen, the intra-abdominal pressures may increase to cause abdominal compartment syndrome. If there is evidence of significant venous congestion of lower limbs after closure, then an abdominal wall silo should be left as a laparotomy at the site of the abdominal incision, as for gastroschisis repair. This may be closed a few days later.

Anesthetic Considerations

Management of pulmonary hypertension and pulmonary insufficiency and the timing of surgery are primary considerations in these neonates. Surgical repair should only be performed in physiologically stable neonates, ideally when inotropic support is no longer required and the neonate has been weaned off ECMO, usually at 2–6 days after birth [141]. Surgery should be postponed if the child becomes unstable during transport to the OR or before surgery begins. Transfer of the neonate with severe CDH carries considerable risk of complications. The team should be prepared for major cardiorespiratory problems with skilled staff and equipment immediately on hand. Some units perform surgery in the NICU, but this remains a contentious issue (see Chap. 13) [168].

A balanced anesthesia technique that includes opioids such as high-dose fentanyl 20–50 mcg/kg, muscle relaxants, and an inhalational anesthetic should be used to preclude a pulmonary hypertensive crisis. Nitrous oxide should be replaced with air at an appropriate oxygen saturation.

The ventilatory strategy should be the same as in NICU but logistical challenges often exist due to the quality of the theater ventilator compared with the NICU machine. A TIVA technique is required for the child receiving HFOV or who depend on ECMO. Central venous access should be femoral in origin aiming to preserve cervical vessels if ECMO is indicated. Invasive monitoring should be continued from the NICU, with transcutaneous carbon dioxide monitoring to supplement direct measurement of arterial $PaCO_2$, particularly in MIS.

Surgical repair is usually uneventful and blood loss is usually limited. Special precautions are required if the child remains on ECMO. Hypotension usually responds to fluid boluses of 10–20 mL/kg balanced salt solution or an increase in the infusion rates of inotropes. Hypotension in the presence of an increasing difference between the pre- and postductal SpO_2 values may indicate an intraoperative pulmonary hypertensive crisis. Simple interventions include increasing FiO_2, increasing depth of anesthesia, opioid administration, and correction of the acidosis that are usually effective. iNO should be available in the event of a pulmonary hypertensive crisis unresponsive to these measures. Deteriorating oxygenation intraoperatively requires exclusion of a pneumothorax on the contralateral (good lung) side or endobronchial intubation must be excluded. At the conclusion of surgery, the neonate should be transferred back to the NICU; the duration of postoperative ventilation is determined by the severity of pulmonary hypoplasia and pulmonary hypertension.

Abdominal Surgery

Inguinal Hernia

Inguinal hernias occur commonly with a childhood incidence of 0.8–4.4%. Males are affected 8–10 times more frequently than females. Premature infants have an increased risk of hernias with an incidence of 13% in neonates born at <32 weeks' gestational age (GA) and 30% in infants <1 kg

birth weight [174]. This group also has an increased risk of complications such as obstruction and incarceration. Inguinal hernia is also associated with cystic fibrosis, connective tissue disorders, and abdominal wall defects.

Pathophysiology

Inguinal hernias result from the failure of obliteration of the patent processus vaginalis (PPV), which develops during testicular descent. Up to 50–80% of neonates may have a PPV and remain asymptomatic until bowel or other intra-abdominal contents enter this sac. When that occurs, it is classified as an inguinal hernia. The right side is more frequently affected (60%) than the left, with 10–15% of cases occurring bilaterally (with a greater incidence in infants).

Diagnosis

An inguinal hernia is diagnosed clinically with the history or presence of a groin swelling (Fig. 9.8). This may extend into the scrotum on the ipsilateral side. The testis should also be palpated during examination, to separate from a groin swelling. The hernia may contain bowel, omentum, or in the case of females, an ovary. Examination should ensure that the hernia is reducible; if the hernia is irreducible (i.e., incarcerated), then the hernia immediately becomes a surgical emergency. The majority (60%) of incarcerated inguinal hernias occur in the first 6 months of life.

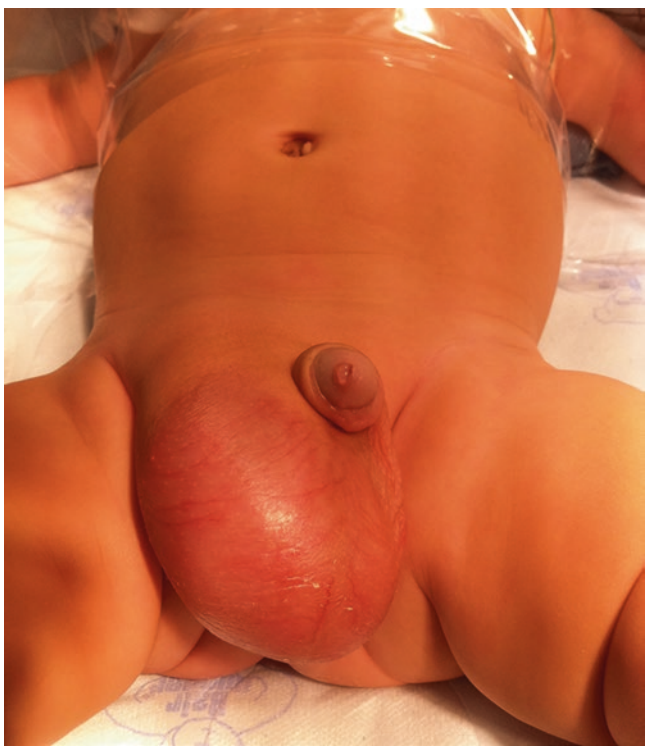

Fig. 9.8 Inguinal hernia in a neonate. Close-up of a right inguinal hernia (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

Surgical Management

Inguinal hernias require surgical closure of the PPV. In many centers, hernia repair is performed as an open procedure via an inguinal incision with ligation of the sac after separating it from the vas and testicular vessels. Care must be taken to fully mobilize and ligate the sac to prevent recurrence while preserving the vas and vessels with minimal surgical trauma. The duration of anesthesia and surgery for inguinal hernia repair in neonates is greater than in older children. The risks of recurrence or testicular atrophy are greater in neonates, particularly if the hernia has become incarcerated.

Laparoscopic repair may also be performed with the closure of the internal ring with a nonabsorbable suture. This technique allows the contralateral side to be assessed and repaired if indicated, which may be particularly beneficial in infants as the incidence of bilateral hernia or contralateral PPV is 60% in this age group. There is less dissection of the cord structures, which may result in less damage; laparoscopic hernia repair in infants is a safe procedure with a small complication rate, although long-term outcomes are not yet clear [175–177]. The laparoscopic approach is feasible even in very small neonates, although the ability to tolerate carbon dioxide insufflation is an important factor, and the procedure may be more challenging technically in the very premature or low-birth-weight neonates. Instead of carbon dioxide insufflation, some advocate gasless laparoscopy in neonates, thereby obviating the cardiorespiratory effects of a carboperitoneum [178]. There is no consensus in the literature as to the best surgical approach; however, delaying neonatal inguinal hernia repair until ready for same-day discharge may be preferable [179].

Anesthetic Management

The timing of surgery in neonates who require hernia repair remains controversial, particularly in premature neonates; the younger the neonate, the more susceptible they are to postoperative apneas as well as surgical complications. This has to be balanced with the risk of incarceration if surgery is delayed. Many centers plan surgery for premature infants near the time of discharge from the hospital, and others delay surgery until after discharge to reduce the potential for postoperative apnea and the need for prolonged postoperative ventilation [180].

An analysis of data from prospective studies of former preterm infants undergoing hernia repair under general anesthesia in the mid-1980s and late 1990s suggested that the probability of postoperative apnea in premature infants was <1% at PCA 56 weeks, with negligible risk of postoperative apnea at 60 weeks' PCA. The risk factors for postoperative apnea were gestational age at birth, postconceptional age, ongoing preoperative apneas, and anemia (hematocrit <30%) [64]. Factors that may reduce the frequency of apneas in premature infants after general anesthesia include regional

block (spinal anesthesia) without sedation, an ilioinguinal/iliohypogastric nerve block, administration of intravenous caffeine 10 mg/kg, and the avoidance of neuromuscular blockade or potent opioids [63, 181]. Respiratory events after sevoflurane and desflurane anesthesia occur with similar frequencies in premature neonates [182]. Current practice guidelines recommend postoperative apnea monitoring for neonates/infants who are full term but less than 44 weeks' PCA and infants who were premature at birth (e.g., ≤37 weeks' gestation) and who are less than 60 weeks' PCA, although it has been suggested that this guidance could be relaxed to 46 weeks for former preterm infants who are without other risk factors for postoperative apnea [183].

Spinal or caudal epidural anesthesia as a sole technique may be associated with fewer postoperative respiratory complications than general anesthesia but spinal has a significant failure rate [183, 184]. During the last decade, concern has increased regarding the possible neurotoxicity from general anesthesia in neonates and infants (see Chap. 18). The GAS study (general anesthesia versus spinal anesthesia for infants undergoing hernia repair), a randomized multicentered trial, completed neurodevelopmental follow-up at 5 years and found no significant difference in psychomotor scores between regional and general anesthesia [185, 186], although the infants were exposed to a single anesthetic for about 1 h. Since such an exposure reflects the median exposure to general anesthesia during surgery in infants, these results likely support the safety of single anesthetic exposures in neonates and infants [187].

Pyloric Stenosis

Pyloric stenosis occurs in 1–3:1000 births and is four to five times more common in males than females and more commonly in firstborn males. The etiology of pyloric stenosis has been elusive, although there is some evidence for a genetic basis for the disease, feeding practices, erythromycin exposure postnatally (or prenatally), sleeping position (prone increases the risk), and possibly infectious moieties [188–191]. The age at which pyloric stenosis presents has been gradually decreasing. Currently, most cases present at 2–5 postnatal weeks, after several days of projectile vomiting [192–194]. Pathological hypertrophy of the inner layer of smooth muscle in the pylorus results in gastric outlet obstruction, which leads to the projectile nature of vomiting.

Pyloric stenosis is usually an isolated defect. However, in some cases, it is associated with genetic syndromes including Cornelia de Lange and Smith-Lemli-Opitz syndromes as well as chromosome 8 and 17 translocations and (partial) trisomy 9 [189].

Diagnosis

The classic symptom of pyloric stenosis is non-bilious projectile vomiting. Term infants are predominantly affected, although pyloric stenosis does occur in premature infants. The diagnosis may be confirmed by clinical examination with visible gastric peristalsis and a palpable pyloric "tumor." These signs may be more clearly demonstrated with a "test feed." The classical biochemical picture is one of dehydration with hypochloremic metabolic alkalosis due to loss of gastric acid. Total body potassium may be depleted due to renal compensation and tubular reabsorption of hydrogen and sodium ions and water in exchange for potassium. If the vomiting continues unabated, the neonates become dehydrated, prompting ADH to cause renal reabsorption of water and sodium at the expense of hydrogen and potassium ions, resulting in "paradoxical aciduria" in the presence of metabolic alkalosis. However, mounting evidence suggests that neonates with pyloric stenosis present earlier in their disease process, resulting in less severe electrolyte imbalance in the past decade [194, 195]. As a result of the less severe electrolyte imbalance and the increasing reliability of ultrasound to delineate both the thickness and length of the pylori (with a sensitivity of 100% and specificity of 98%), ultrasound has supplanted the electrolyte panel as the cardinal criterion for diagnosis of pyloric stenosis [192–194, 196].

Medical Management

This disorder is a medical, not surgical, emergency. Initial management consists of rehydration and correction of any electrolyte imbalance. Depending on the severity of the fluid and electrolyte derangements, 24–48 h preparation may be required, although affected neonates are reaching pediatric surgeons earlier in the disease process currently, reducing the time required to correct electrolyte disturbances, if they even develop disturbances at all [194, 195]. Surgical intervention should not be undertaken until the neonates have been stable medically and the plasma bicarbonate is <28 mmoL/L and plasma chloride >100 mmoL/L. Infants with severe dehydration may require an initial fluid bolus of 20 mL/kg 0.9% saline, followed by maintenance fluid with 5–10% dextrose and 0.45% saline, provided the plasma sodium is in the normal range. The stomach should be decompressed with a nasogastric tube, and gastric losses replaced ml for ml with intravenous 0.9% saline and 10 mmol KCL per 500 mL. Potassium should be added to maintenance fluids only after the infant begins to pass urine [192].

Surgical Management

The traditional operation for pyloric stenosis is Ramstedt's pyloromyotomy, an extramucosal longitudinal splitting of the hypertrophied muscle (Fig. 9.9). This was originally described using an upper midline incision but many centers now use a supraumbilical approach to provide better cosmesis. Laparoscopic pyloromyotomy is also widely performed, with a randomized controlled study and early meta-analysis demonstrating some benefits from this approach (reduced

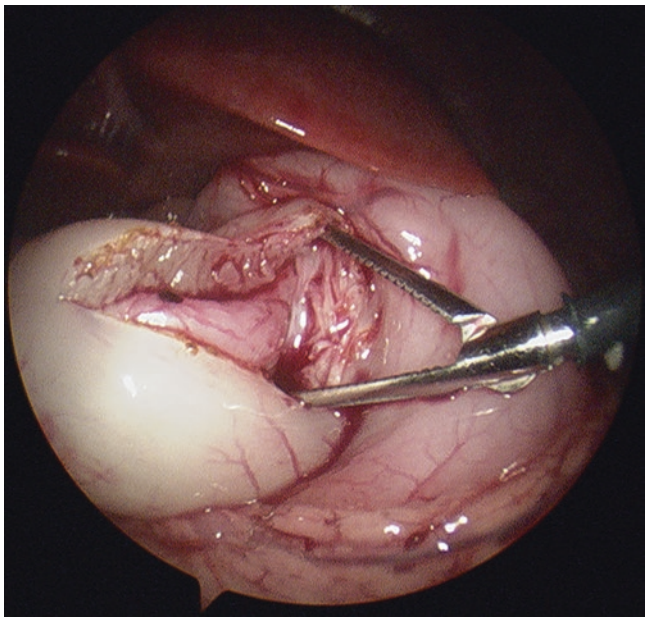

Fig. 9.9 Pyloromyotomy. The thickened muscle layer of the pylorus can be seen, incised down to the mucosa. To ensure the muscle has been completely incised, laparoscopic alligators distract the walls of the muscle layer. Note the very thick muscular wall that has been peeled off the pylorus. The liver edge is present immediately above the pylorus at the top of the figure (Courtesy of Dr. K. Bass, Division of Pediatric Surgery, Women and Children's Hospital of Buffalo, Buffalo, NY)

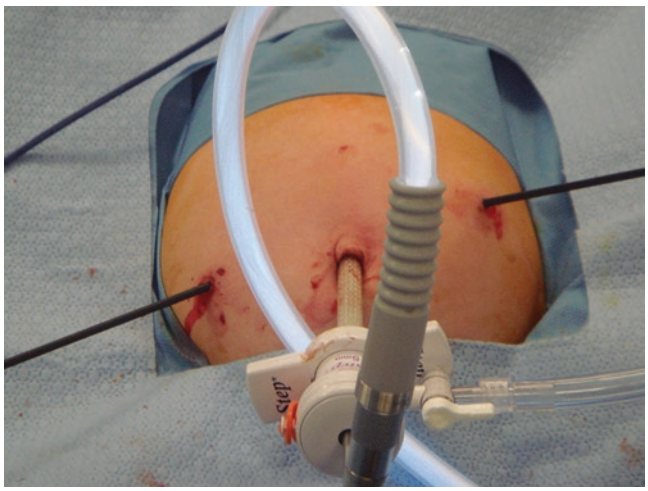

Fig. 9.10 Laparoscopic insufflation of the abdomen. The neonate's head is at the top of the figure and the legs are at the bottom. During laparoscopic pyloromyotomy, three ports are placed: the largest trocar (5 mm Mini Step) is inserted through the umbilicus, whereas the two smaller graspers are passed laterally through simple skin incisions. The peritoneal cavity is insufflated with carbon dioxide to ~8 mmHg pressure

time to full feed and length of stay), without an increase in postoperative complications although the debate continues regarding the superiority of the laparoscopic over the open approach for pyloric stenosis [6, 197, 198] (Fig. 9.10). Whether laparoscopic approach includes multiple incisions, a single incision, or a microlaparoscopic (<2 mm diameter instruments) approach [199], it would appear to be the evolving standard for pyloromyotomy.

Anesthetic Considerations

Surgery should only be scheduled after the fluid status and electrolyte concentrations (including pH) have been normalized; otherwise, the child will be at increased risk of postoperative apnea, arrhythmias, and circulatory instability. Previously a nasogastric tube was routinely inserted as part of medical management before arrival in the operating room. It has been proposed that constant gastric drainage in the absence of milk feeding may worsen electrolyte balance and be unnecessary in the preoperative period [200]. Depending on institutional practice, a nasogastric tube may be in situ before arrival in the operating room. Regardless, the stomach should be emptied by passing a large bore tube into the stomach before induction of anesthesia to minimize the risk of gastric fluid regurgitation and pulmonary aspiration. "Four quadrant" aspiration is an appropriate technique accomplished by rolling the neonate to the left and the right while aspirating the NG tube. An index of suspicion should be maintained that the NG tube could be blocked or malpositioned. Ultrasound assessment of gastric contents has been studied in infants with pyloric stenosis, demonstrating that a qualitative assessment of stomach contents can be made quickly and easily before induction of anesthesia [201].

The traditional induction technique is a modified RSI, avoiding cricoid pressure but gentle mask ventilation continues with 100% oxygen until laryngoscopy begins. Surveys of experienced pediatric anesthesiologists reveal that fewer than 50% apply cricoid pressure to infants with pyloric stenosis [202]. There is in fact no evidence that cricoid pressure actually prevents aspiration pneumonitis [203]. It has also been demonstrated that cricoid pressure is difficult to apply correctly in young infants and may distort the airway, complicating laryngoscopy and tracheal intubation [28, 204]. The modified RSI as described is commonly practiced in neonates and young infants with full stomachs to prevent desaturation during the interval between loss of consciousness and securing the airway.

The anesthetic regimen for pyloric stenosis involves offsetting two conditions: to facilitate rapid tracheal intubation and recovery from anesthesia in ~30 min, the duration of surgery. In preparation for tracheal intubation, a hockey-stick curve to the tracheal tube (a 3.5 uncuffed or 3.0 Microcuff® tube) molded with a stylet to maintain its shape ensures a rapid and successful tracheal intubation, particularly in the absence of a muscle relaxant.

Intravenous induction with propofol can be used in combination with opioid and a muscle relaxant. With the black box warning by the Food and Drug Administration in the

USA, many clinicians avoid succinylcholine in male infants and young children. If a nondepolarizing relaxant is used (most commonly rocuronium), then a small dose is often administered to preclude difficulty when antagonizing with an anticholinesterase after brief surgery [205, 206]. Alternately, sugammadex can be used to antagonize neuromuscular blockade with rocuronium (in a dose of 2–4 mg/kg) even in neonates [207, 208], although it is expensive, not available in every country, and not approved for use in neonates in many countries.

Balancing the hesitation to use a nondepolarizing muscle relaxant when the surgeon can complete the surgery rapidly, other regimens may be considered. A short-acting IV opioid such as fentanyl 1–2 mcg/kg or remifentanil followed by a large induction dose of propofol (3–5 mg/kg) has been used to secure the airway. Alternately, others administer sevoflurane in oxygen while preoxygenating the neonate [209], judiciously timing a bolus of IV propofol (2–4 mg/kg) ± a short-acting opioid, to provide optimal intubating conditions.

Delayed emergence after pyloric stenosis is a common and perplexing problem. This has been attributed to several causes including the intraoperative use of opioids. Although some insist on administering a short-acting opioid such as fentanyl or remifentanil, infiltrating the laparoscopic wounds with local anesthetic is quite effective [210, 211]. A regional block such as a rectus sheath block or epidural has also been effective after open pyloromyotomy [212, 213]. IV or rectal acetaminophen also provides mild pain relief perioperatively, without delaying emergence [214]. Despite avoiding opioids entirely, many continue to experience a very slow emergence from anesthesia and time to extubation after this surgery. Other possible causes for the delayed emergence include the use of nondepolarizing muscle relaxants, although one retrospective study disputed this claim, noting that 0.7 mg/kg rocuronium minimally delayed the time to transport to recovery compared with succinylcholine, after a propofol/sevoflurane anesthetic [205, 206, 215]. Insufflating the abdomen in neonates and infants does not require the use of a nondepolarizing muscle relaxant, although it does require a deep level of anesthesia, which often implies large concentrations of inhalational agents and controlled ventilation. Pharmacokinetically, desflurane with or without nitrous oxide is the optimal maintenance inhalational anesthetic to facilitate a rapid emergence and extubation after pyloromyotomy (editor's note) (see Chap. 3) [216]. At least one MAC of desflurane is required during insufflation, which corresponds to an end-tidal desflurane concentration of 9.6% in this age group [217]. To reduce the concentration of inhalational anesthetic required, remifentanil may be added [210]. Antiemetics are not indicated in neonates as the incidence of postoperative vomiting in this age group is very small and surgeons may use ongoing vomiting as a sign of an incomplete repair or complication [218]. After the pneumoperitoneum is released, the inspired concentration of desflurane is reduced to ~3%. When the skin incisions are closed and dressed, all anesthetics are discontinued.

Intestinal Atresias

Congenital intestinal atresia or stenosis can occur at any point along the gastrointestinal tract. The neonate presents with intestinal obstruction, the timing, and specific presenting features relating to the level of the obstruction [219–221].

Pyloric Atresia

Pyloric atresia is an extremely rare condition (1:100,000 live births) representing 1% of intestinal atresias. Up to 30% of patients have other associated anomalies including epidermolysis bullosa, aplasia cutis congenita, and esophageal atresia. Presentation is with non-bilious vomiting with a single gastric bubble on abdominal X-ray and no distal gas. Surgery involves a laparotomy to either excise the obstructing membrane or perform a bypass procedure (gastroduodenostomy or gastrojejunostomy) to restore intestinal continuity. The practical considerations are similar to those for duodenal atresia.

Duodenal Atresia

Duodenal atresia or stenosis occurs in 1:5,000–1:10,000 live births with a male preponderance. Half of the patients have associated anomalies, commonly trisomy 21 (30–40%), malrotation (30–40%), and cardiac anomalies (20%). Anorectal and genitourinary anomalies, esophageal atresia, and Meckel's diverticulum are also associated with duodenal atresia and, more rarely, biliary anomalies. Up to 45% of babies are born prematurely [219]. Duodenal atresia may be classified as follows (Table 9.3).

Embryology

Duodenal atresia may be due to abnormal embryological development of the duodenum, pancreas, and biliary tree. Proposed mechanisms include failure of recanalization of the duodenum during the 8–10th week and altered rotation of the ventral analogue of the pancreas resulting in an annular pancreas. The obstruction is distal to the ampulla in the majority of patients (60–85%). An alternative theory common to all atresias is the possibility of a vascular accident (see jejunoileal atresia below).

Table 9.3 Classification of duodenal atresia

Type I—mucosal diaphragmatic membrane
Type II—short fibrous cord connecting two ends of the atretic duodenum
Type III—complete separation of the two ends of the duodenum

Diagnosis

Polyhydramnios occurs in 33–60% of pregnancies and antenatal ultrasound may demonstrate a "double bubble." Cardiac abnormalities may also be detected at this time. Postnatally the baby develops bilious vomiting in the majority, although vomiting may be non-bilious if the atresia is proximal to the ampulla. Abdominal X-ray shows the characteristic double bubble with an absence of gas distally. Distal gas may occasionally be seen if the atresia is periampullary with the main pancreatic and accessory duct opening on either side. Gas can then travel via the biliary tree into the distal intestine. The antenatal and abdominal X-ray findings are less clear in duodenal stenosis, which may present later depending on the degree of obstruction. The differential diagnosis of duodenal atresia is malrotation and volvulus, which can have catastrophic consequences if not detected. If there is any doubt about the diagnosis, for instance, if there is distal gas or no antenatal history, an urgent upper gastrointestinal contrast study should be performed to exclude malrotation. If doubt still remains, then an urgent laparotomy should be performed.

Management

The ultimate management for this congenital defect is surgical, although the neonate should initially be resuscitated and stabilized before proceeding. A nasogastric tube should be passed, losses replaced, and maintenance fluids infused. Preoperative workup includes a thorough clinical examination and echocardiography to exclude associated anomalies.

Outcomes

The mortality and morbidity associated with duodenal atresia are small. Early operative mortality is less than 5%, predominantly due to complex cardiac anomalies, and long-term survival is 90%. Morbidity associated with this condition includes gastroesophageal reflux disease, delayed gastric emptying, peptic ulcer disease, duodenal stasis, and blind loop syndrome or megaduodenum, and adhesive small bowel obstruction. These complications may not be apparent until much later in life.

Surgical Considerations

A laparotomy and duodenostomy (either end-to-side or Kimura diamond anastomosis) are the primary procedures performed. Access is via a supraumbilical transverse or umbilical (Bianchi) incision. The minimally invasive laparoscopic approach is feasible and safe and is being used in some centers, although liver retraction and exposure of the duodenum can be difficult especially in a small infant or in the presence of hepatomegaly. The laparoscopic approach may benefit earlier return to full enteral feeding and reduced analgesic requirements [222]. It is important to check that a second duodenal web is not present (seen in 1–3% of cases), and there are no distal atresias. Intestinal rotation should be checked and malrotation corrected if present. The gall bladder should be visualized for bile. Some surgeons choose to leave a transanastomotic tube in situ although full enteral feeds are usually achieved without this maneuver.

Anesthetic Considerations

Anesthetic considerations relate mainly to anesthesia for laparotomy in the presence of upper gastrointestinal obstruction and coexisting abnormalities, especially complex cardiac anomalies, and prematurity. If the child is otherwise well, the aim should be to extubate at the end of the procedure.

Jejunal/Ileal Atresia

Small bowel atresia or stenosis is a common cause of neonatal intestinal obstruction occurring in 1:3,000 live births [220]. Stenosis is due to a localized narrowing of the lumen without loss of continuity in the intestine or mesentery (Fig. 9.11). Small bowel atresias are classified into four major types [221, 223] (Table 9.4).

Types II and IIIa occur most commonly. There may be a family history, especially in type IIIb atresia. Multiple atresias are not uncommon, with up to 67% of jejunal atresias

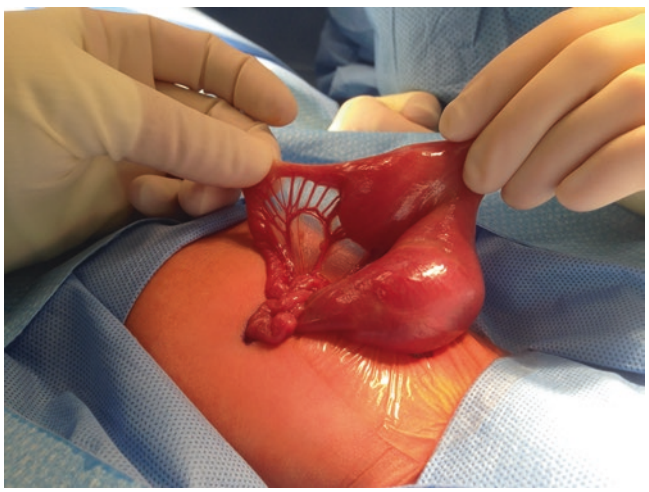

Fig. 9.11 Jejunal atresia. At laparotomy, normal jejunum is held up on the right side of the photo. The jejunal lumen narrows at the atresia in the middle of the photograph, with a very small lumen thereafter. The mesentery, which supplies blood to the bowel, is intact (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

Table 9.4 Classification of small bowel atresias [221]

Type I—a membrane or web
Type II—blind ends separated by a fibrous cord
Type IIIa—disconnected blind ends
Type IIIb—absence of the superior mesenteric artery resulting in the "apple peel," "Xmas tree," or "Maypole" abnormality
Type IV—multiple segment atresia ("string of sausages")

and 25% of ileal atresias having further distal atresias. Chromosomal abnormalities are much less common in the more distal atresias compared with duodenal atresia although 12% of patients with ileal atresia will also have cystic fibrosis. These patients should have genetic screening and a sweat test performed at an appropriate time postoperatively. There is an association between gastroschisis and small bowel atresias.

Embryology

The most popular theory is that the atresia results from an intrauterine "vascular accident." Interruption of the blood supply results in sterile necrosis and resorption of affected segments. Multiple causes of vascular interruption have been proposed including fetal intussusceptions, midgut volvulus, thromboembolic occlusions, transmesenteric internal hernias, and incarceration as the result of an abdominal wall defect. The use of methylene blue in amniocentesis for twin pregnancies has also been implicated. The insult is believed to occur after week 11 of gestation. This is supported by the findings of bile, lanugo hair, and squamous epithelial cells from swallowed amniotic fluid distal to the atresia.

Diagnosis

Polyhydramnios may be present prenatally although it is less common, the more distal the obstruction. Dilated bowel loops may be present on antenatal scans. Postnatally, these lesions present with signs of intestinal obstruction including vomiting (usually bilious), abdominal distension, and failure to pass meconium. Respiration may be compromised if the distension is severe, and the neonate may require preoperative respiratory support (and hence postoperative support). A plain abdominal X-ray will show dilated bowel loops (number depending on the level of the obstruction). A contrast enema may be performed preoperatively to exclude the differential diagnoses of meconium ileus, Hirschsprung's disease, and coexisting more distal atresias. Ten percent of neonates present with meconium peritonitis due to antenatal perforation; calcification or meconium pseudocyst may be seen on abdominal X-ray.

Outcomes

The long-term survival for patients with jejunoileal atresia is 84% [224]. The primary cause of morbidity and mortality is short bowel syndrome or intestinal failure requiring total parenteral nutrition, with the associated risk of sepsis and liver disease.

Medical Management

As with all neonatal intestinal obstruction, the initial goal is to stabilize the neonate by decompressing the stomach with an NG tube, nil by mouth, intravenous resuscitation, and maintenance fluids. Investigations should be performed as described above.

Surgical Considerations

The most common surgical procedure to localize the atresia is a laparotomy. Once it has been identified, the atresia is excised with a primary anastomosis. There may be a significant discrepancy in size between the proximal and distal ends of the atresia, making an end-to-end primary anastomosis challenging. Despite this, a 7:1 discrepancy can be accommodated with meticulous technique and 7-0 suture material. If bowel length is not a problem, then the dilated bowel can be resected back to a more reasonable caliber. If a type IIIb "apple peel" atresia is discovered, particular care must be taken to avoid compromising the retrograde vascular supply from the marginal colic arteries to the remaining distal small bowel. Problems with the absorption of feed and short bowel syndrome are also more common with this type of atresia [225]. This has been attributed to the severity of the vascular insult. Given the high risk of multiple atresias, the continuity of the distal bowel should be confirmed by passing a small balloon catheter through the lumen and flushing with either air or saline before the anastomosis is performed. If the neonate is unstable or the distal bowel is significantly compromised, then a proximal stoma and mucous fistula are preferred as a temporizing measure, with the restoration of bowel continuity restored when the neonate has fully recovered. The remaining length of small bowel should be measured and documented to help predict and manage neonates with possible short bowel syndrome.

Anesthetic Considerations

These are the same as for any neonate undergoing laparotomy. However, postoperative ventilation may be required after prolonged laparotomy and a significant fluid shift. Long-term vascular access may be required for parenteral nutrition.

Colonic Atresia

This is a very rare cause of intestinal obstruction and represents <10% of all intestinal atresias. A vascular insult is the likely cause of these atresias. These occur when closing abdominal wall defects especially gastroschises secondary to localized vascular interruption. Applying the Grosfeld classification, most are type IIIa or type I. Associated proximal atresias are common (22%), and right-sided atresias are associated with Hirschsprung's disease.

Diagnosis

Colonic atresia presents with symptoms of distal obstruction, including abdominal distension, failure to pass meconium, and bilious vomiting. Multiple loops of distended bowel on plain abdominal X-ray confirm the presence of distal bowel

obstruction. A hugely distended loop of bowel is often present because of the closed loop obstruction in the presence of a competent ileocecal valve. Contrast enema confirms the location of the most distal atresia.

Management

Preoperative management is the same as for all neonates with intestinal obstruction. This has been discussed above. Early surgical intervention is essential, as the mortality from perforation may reach 100% if surgery is delayed for more than 4 days.

Surgical Considerations

Surgical options are laparotomy with either formation of decompressing colostomy or primary anastomosis. Although anastomotic leakage is frequent and sepsis has been reported previously in neonates undergoing primary anastomosis, more recent reports support this approach. Hirschsprung's disease should be considered if an anastomotic leak is detected. A stoma is preferred to direct anastomosis if resection to bowel with a more appropriate caliber results in short bowel syndrome. As per jejunal/ileal atresias, the distal bowel must be assessed intraoperatively by flushing with air or fluid to identify additional atresias.

Meconium Ileus

Meconium ileus results from the obstruction of the distal small bowel due to thick inspissated meconium. The majority (90%) of cases can be attributed to intestinal and pancreatic dysfunction secondary to cystic fibrosis (CF). Up to 25% of neonates with underlying cystic fibrosis will present with meconium ileus. Once the obstruction has been successfully treated, the infant must be tested for CF. The presence of meconium ileus does not predict a worse, long-term outcome from CF, although almost all children with meconium ileus develop pancreatic insufficiency and will require pancreatic enzyme replacement when feeds are introduced [226]. It is important to involve the respiratory physicians early, even though clinical lung disease is very uncommon in neonates.

Diagnosis

Simple meconium ileus presents with distal intestinal obstruction. Plain abdominal X-ray shows multiple loops of dilated bowel with a "soap bubble" appearance in the right lower quadrant (Neuhauser's sign). This results from the mixing of air and the tenacious meconium. A contrast enema will show a microcolon with pellets of meconium in the terminal ileum.

Complications occur in 50% of cases. Perforation may occur in the antenatal period if the proximal bowel becomes ischemic or perforates secondary to a volvulus. This will lead to meconium peritonitis and possibly a giant pseudocyst. The neonate may present with a large abdominal mass or meconium may be passed vaginally or be evident in a patent processus vaginalis in the scrotum. Calcification is often evident on a flat plate (X-ray) of the abdomen. Intestinal volvulus or atresias may also occur.

Outcomes

Outcomes are slightly more favorable in simple meconium ileus with a 1-year survival of 92% compared with 89% in complicated meconium ileus [226].

Management

The usual resuscitative measures should be performed in conjunction with broad-spectrum intravenous antibiotics, and the neonate should remain nil by mouth. If the diagnosis is consistent with simple meconium ileus, the obstruction may be relieved by nonoperative measures using a hyperosmolar contrast enema (Gastrografin® or Omnipaque®), which may be repeated. Operative intervention is indicated for enema failures and complicated meconium ileus.

Surgical Considerations

Surgical options include manual disimpaction at laparotomy either via a proximal enterotomy or with the intraluminal injection of 4% *N*-acetylcysteine. A combination of these two may be required to fully clear the impacted plugs. If this is not possible, a distal loop or double-barreled stoma should be performed, although this is rarely required. Primary laparotomy is performed in complicated meconium ileus; the options are resection and anastomosis or, alternatively, stoma formation. It is essential to ensure that the obstruction into the microcolon is relieved completely if a stoma is not performed. Additional *N*-acetylcysteine via a nasogastric tube is sometimes advocated. The stoma should be closed as soon as possible to avoid excessive sodium losses from the gastrointestinal tract and from sweat.

Anesthetic Considerations

Management is the same as for any neonatal laparotomy including fluid resuscitation and respiratory support according to clinical requirements. Hypertonic enemas increase the risk of hypovolemic shock in neonates as fluid becomes sequestered in the gut. Fluid may need to be replaced throughout the intra- and postoperative periods to replace the preoperative and intraoperative fluid losses. A sweat test should be performed early in the postoperative period to establish the diagnosis of CF. Fortunately, respiratory complications are uncommon in the neonatal period.

Malrotation and Volvulus

Malrotation is a congenital anomaly of the bowel in which an abnormal position and fixation of the midgut shorten the mesenteric base, predisposing to a volvulus [227]. The incidence is 1:500–1:1000 based on postmortem studies. The

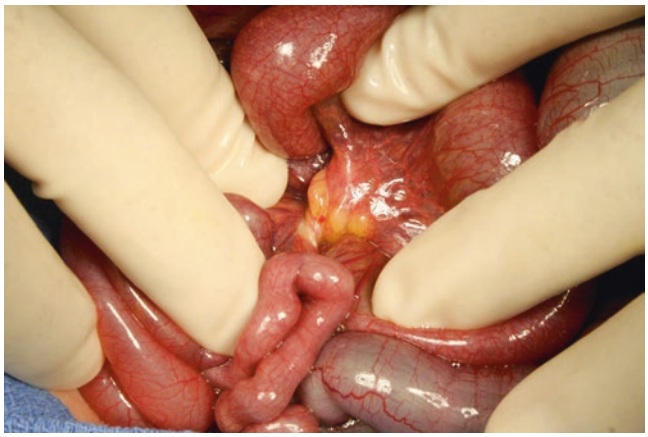

Fig. 9.12 Midgut volvulus. At the ends of the gloved fingers (center of the photo), a tightly twisted midgut (covered in yellow fat) volvulus is evident (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

incidence based on symptomatic presentation is 1:6000 live births or may be discovered incidentally. Other anomalies associated with malrotation include intestinal atresias, such as duodenal web, abdominal wall defects, congenital diaphragmatic hernia, imperforate anus, cardiac abnormalities, Meckel's diverticulum, and trisomy 21. Males are twice as likely to present in the neonatal period as females. Malrotation with midgut volvulus constitutes a true surgical emergency as the consequences are potentially catastrophic with loss of the entire small intestine (Fig. 9.12).

Embryology

The traditional theory of intestinal development has the small bowel undergoing a counterclockwise 270° rotation during the 6th–10th week of gestation as it returns to the abdomen from the physiological hernia. During weeks 10–12, the bowel undergoes fixation. Failure of these processes is termed "malrotation." This anomaly results in a shortened mesenteric base with the D-J flexure in an abnormal right-sided and low position, with a high position of the cecum, and a tendency of the small bowel to twist around the mesenteric base (volvulus). This causes obstruction of the blood supply and lymphatic drainage to the small bowel (as well as luminal bowel obstruction), which can lead to ischemia to ischemia with necrosis of the entire midgut. It is imperative that malrotation with volvulus is identified in a timely manner and corrected before necrosis of the bowel occurs.

Diagnosis

The majority of neonates with malrotation present in the first month of life (50–75% of cases). The most common presenting symptom is bilious vomiting, although some may have non-bilious vomiting. Other signs including abdominal tenderness or distension, diarrhea or constipation, and lethargy present less commonly. Systemic compromise and blood in the stools are later signs of volvulus in which significant ischemia has already occurred. Abdominal X-ray may be deceptively normal. The gold standard for diagnosis is an upper GI contrast study, which demonstrates duodenal obstruction when volvulus has occurred. The appearance is that of a "bird's beak," coiled, or "corkscrew." The normal position of the D-J flexure is to the left of the midline, at or above the level of the pylorus. For uncomplicated malrotation in the absence of a volvulus, the contrast study demonstrates the abnormal position of the D-J flexure to the right of the midline. The position of the cecum is variable, rendering it an unreliable sign of a malrotation. CT or ultrasound may demonstrate reversal of the normal position of the superior mesenteric artery (SMA) relative to the superior mesenteric vein (SMV), with spiraling of these vessels if volvulus has occurred. Ultrasound can be used to track the course of the duodenum and D-J flexure. Urgent laparoscopy or laparotomy is required if the diagnosis remains in doubt [228].

Outcomes

Malrotation with volvulus may lead to ischemic necrosis of the entire midgut. Accordingly, it is essential that a pediatric surgeon assess all neonates with bilious vomiting in a timely manner to prevent ischemia of the bowel. The mortality rate is ≤10%. Short bowel syndrome (see Gastroschisis for further discussion) occurs in 18% of neonates with volvulus. Complications of surgery include adhesive bowel obstruction in up to 20% and recurrent volvulus in 6% of neonates. Those with malrotation may develop intestinal dysmotility at a later date.

Management

A high level of clinical suspicion must be present when a neonate presents with bilious vomiting. The outcome after volvulus depends on time so early diagnosis and intervention are critical. Initial resuscitation should be undertaken before an urgent upper GI contrast study. Immediate surgical intervention is indicated if malrotation with volvulus is diagnosed. For those in whom malrotation without volvulus is confirmed or suspected, optimal management is controversial. Knowing there is a substantive risk for future volvulus, many surgeons advocate a semi-urgent surgical procedure to assess the mesenteric base and proceed to correction, if appropriate.

Surgical Considerations

The classic surgical approach is Ladd's procedure with derotation of the volvulus. In this procedure, the duodenum is mobilized, the mesenteric base is widened, and the D-J flexure and the small bowel are mobilized to the right of the abdomen and the cecum and large bowel to the left. If obstructing

peritoneal bands (Ladd's bands) are identified, they are divided. Many surgeons also perform an appendicectomy as the cecum is abnormally located in the left upper quadrant. Ladd's procedure has been classically performed via laparotomy or more recently by laparoscopy, the latter providing a potentially less invasive means to assess the stability of the mesentery. If technical factors preclude the latter approach, then early conversion to an open technique must occur. The role of laparoscopy for correction of volvulus in a neonate remains controversial; however, there is increasing evidence of the safety and benefits of this approach and this is becoming more commonly performed [228–231]. The long-term outcomes for the laparoscopic approach however remain unclear. Despite a reduced risk of future adhesive bowel obstruction, the risk of recurrent volvulus remains uncertain.

Derotation of the bowel is often sufficient to restore the blood supply to the midgut and the viability of the bowel. However, if the diagnosis is delayed, the bowel may remain ischemic after derotation, possibly the result of vascular thrombosis in the mesenteric vessels. The surgical options to address the ischemic/necrotic bowel include excision of the necrotic segment, with or without anastomosis, or conservative management with a "second look" laparotomy after 36–48 h to determine whether perfusion of the ischemic bowel has improved. A technique that involves massage of the mesenteric vessels after derotation (to break up clot), and systemic thrombolysis using tissue recombinant tissue-type plasminogen activator (tPA), has been described in two neonates with severe intestinal ischemia due to thrombosis. This resulted in dramatic restoration of bowel perfusion, with subsequent complete recovery of bowel function [232]. If the small bowel is completely necrotic, then withdrawal of care should be explored with the parents.

Anesthetic Considerations

These cases are critical surgical emergencies that must be given priority over all other cases. Surgery must not be delayed. Preoperatively, the status of the neonate may range from relatively healthy to hypovolemic and/or septic shock. In the latter condition, preoperative resuscitation should occur concurrently with the preparation and transfer of the neonate to the operating theater. Group "O"-negative blood should be available if necessary. A nasogastric tube should be passed to decompress the abdomen, and ventilatory support provided as required. If the neonate is in shock or extremis, then anesthesia should be induced using IV ketamine, fentanyl, and/or remifentanil, and the airway secured after with either rocuronium or atropine/succinylcholine [233]. Coagulopathy is common in the presence of necrotic bowel requiring platelets and fresh frozen plasma. Inotropic support with dopamine and/or adrenaline may be required. Invasive monitoring is very useful during this initial resuscitation phase.

If the neonate is stable, maintenance of anesthesia can include fentanyl or remifentanil or a low dose of inhalational anesthesia. Deep inhalational anesthesia must be avoided in critically ill neonates. The surgeon should inform the anesthesiologist when the volvulus is about to be reduced because derotation may lead to acute cardiovascular instability due to the release of lactic acid and other vasoactive compounds. The anesthesiologist should be prepared to manage transient acidosis and hyperkalemia with IV calcium chloride (10–30 mg/kg), bicarbonate, and occasionally salbutamol.

Reperfusion of the bowel is the primary goal. Adequate fluid resuscitation with warmed boluses of Hartmanns or PlasmaLyte solution, albumin, or packed red cells is required based on clinical assessment and monitoring. The fluid requirement may be substantial at this juncture; volumes as great as 50–100 mL/kg may be required. Inotropic support may also be required at this time to support the circulation, active warming of the neonate, and patience and time to assess recovery of the bowel.

If malrotation is identified early, and the child is in good condition preoperatively, it is reasonable to consider extubating the trachea at the end of surgery. The late-presenting infant with necrotic bowel may remain critically ill even after derotation, requiring full support in the intensive care unit until perfusion is restored. Long-term parenteral nutrition may be required in some cases to bridge until the bowel regains full functionality.

Hirschsprung's Disease

Hirschsprung's disease is congenital aganglionosis of the bowel of variable length extending from the anus proximally [234]. This results in a lack of propagation of the intestinal propulsive waves, failure of relaxation of the internal anal sphincter, and functional bowel obstruction. It occurs in 1:4,500–5000 live births with males affected more than females. 80–90% of those with Hirschsprung's disease present in the neonatal period.

Embryology

Hirschsprung's disease is one of the neurocristopathies with presumed failure of the craniocaudal migration of the neural crest-derived neuroblasts, which form the myenteric and submucosal enteric plexuses (which should reach the rectum by week 12 of development). Other theories include failure of neuroblast differentiation, defects in function, or cell death. Varying lengths of bowel are affected, the most frequent pattern being short-segment disease affecting the rectosigmoid region (80%). Long-segment disease occurs when aganglionosis extends proximal to the rectosigmoid region, with total colonic disease in 3–8% of cases. Total intestinal involvement is rare.

Genetics

Hirschsprung's disease is a multigenic disorder with multiple different genes and chromosomal loci implicated, with new genes being continually identified [235, 236]. There appears to be a dysfunction in one of two signaling pathways, which are critical in the development of the enteric nervous system. There is weak and sex-dependent penetrance, with variable phenotypic expression. 10% of patients have a family history (more common in long-segment disease). The RET (receptor tyrosine kinase) proto-oncogene mutation 10q11.2 is present in 50% of familial and 15–20% of sporadic cases and 70–80% of long segment and up to 38% of short-segment disease [235–237]. Currently, genetic profiles are not widely available to assess the disease risk in individuals; however, a further understanding of the complex genetic interplay may lead to novel new treatments including stem cell therapy [236–238].

Hirschsprung's disease occurs in isolation in 70% of cases, but it may be associated with trisomy 21 (5–15% of cases of Hirschsprung's disease), other neurocristopathies (Waardenburg-Shah syndrome (SW4), congenital central hypoventilation syndrome, multiple endocrine neoplasia (MEN) type 2, neuroblastoma, and neurofibromatosis I), other syndromes such as Shprintzen-Goldberg and Smith-Lemli-Opitz, and congenital anomalies such as cardiac, genital, and gastrointestinal anomalies, facial dysmorphism, and cleft palate [234].

Diagnosis

In neonates, the most common presenting symptoms are bile-stained vomiting with failure to pass meconium in the first 24 h of life (94% of normal term infants pass meconium <24 h). This may be associated with poor feeding, abdominal distension, and vomiting. Rectal examination may result in explosive stool and may temporarily relieve the symptoms. Signs of enterocolitis (fever, abdominal distension, and diarrhea) may also be present. Differential diagnoses include the other causes of neonatal distal bowel obstruction discussed in this chapter. An abdominal X-ray may show dilated loops of bowel with an absence of air in the rectum. A distal contrast study may show dilatation of the proximal colon with a change in caliber (transition zone) to normal bowel, but this is not reliable. Rectal biopsies provide a definitive diagnosis for Hirschsprung's disease; the diagnosis is confirmed by the absence of ganglion cells, with altered acetylcholinesterase staining with hypertrophied nerve trunks. It is performed using a suction rectal biopsy in the neonatal period or open biopsy in older children. Anorectal manometry is not usually performed in neonates.

Management

Initial management aims to relieve the functional bowel obstruction either with warm saline washouts or a defunctioning stoma into the ganglionic bowel. A stoma is indicated if the neonate is unwell or has developed enterocolitis and perforation and has a grossly dilated colon or suspected long-segment disease. Hirschsprung's enterocolitis is a potentially fatal complication that must be identified early and managed aggressively to reduce the risk of sepsis, intestinal necrosis, and perforation. Treatment with fluid resuscitation and broad-spectrum antibiotics is required.

Definitive surgery consists of resection of the aganglionic segment, either after initial stoma formation or ideally as a primary procedure. Several "pull-through" techniques have been described, usually performed when the infant is approximately 3 months of age, 5–6 kg weight [239]. The timing and exact procedure performed varies among centers and according to the length of abnormal bowel. Each technique can be performed completely open, or with laparoscopically assisted intra-abdominal dissection and biopsies, or entirely laparoscopically [239, 240].

Surgical Procedures

The first surgical procedure described to address Hirschsprung's disease was the Swenson procedure. This procedure is a low anterior resection of the rectum and aganglionic bowel, with a low anastomosis performed by prolapsing the bowel outside the anus.

The Duhamel procedure was the first alternative operation proposed in which the native rectum remains unchanged and a side-to-side anastomosis is stapled to the ganglionic bowel, which is mobilized and brought down to the presacral space. This requires less rectal dissection and offers a better chance of continence in the long term. It is often the preferred technique for long-segment disease. A retrospective review of open and laparoscopic approaches yielded similar operative time and outcomes [240].

The Soave procedure further minimizes rectal dissection by performing a mucosal dissection in the rectum and leaving a rectal muscular cuff. The original description has been modified to include a formal anastomosis just above the level of the dentate line.

A pure "transanal" pull-through without a laparotomy or laparoscopy has also been reported for Hirschsprung's disease but may not be appropriate for longer-segment disease. Long-segment disease is not always suspected preoperatively, potentially complicating this approach. Other operations have been described, although less frequently reported. There is a paucity of prospective studies that compare the different techniques. Retrospective reviews and meta-analysis show comparable results with no "gold standard" identified [241, 242].

Outcomes

Appropriately managed, Hirschsprung's disease is associated with low mortality, although up to 50% of patients

undergoing surgery develop a complication such as constipation, fecal incontinence, or enterocolitis. Enterocolitis, the most severe complication, can occur in all patients with Hirschsprung's disease, both before and after surgery. It occurs more frequently in those with long-segment disease and those with trisomy 21. Enterocolitis is the primary cause of mortality in children with Hirschsprung's disease and must be identified and managed aggressively. Constipation occurs more frequently after the Duhamel pull-through, whereas incontinence occurs more frequently after the Soave and Swenson procedures. To date, there are no prospective randomized controlled trials that compare the outcomes from the different surgical techniques, although overall complication rates appear to be similar among all approaches.

Surgical Considerations

The transition zone between ganglionic (normal) and aganglionic (abnormal) bowel can vary in length (>20 cm) and demonstrate an irregular margin [243]. It is important to perform an anastomosis between bowel segments with normal ganglion cells without tension or vascular compromise. Time must be allowed regardless of procedure for intraoperative frozen section results of serial biopsies at ascending levels to accurately assess the extent of affected bowel and also assess the anastomotic donut. If long-segment disease is discovered unexpectedly, then many recommend that the pull-through procedure be delayed until formal histology is available.

Anesthetic Considerations

A complete preoperative history should be completed including a history of existing syndromes and anomalies that are associated with Hirschsprung's disease. Definitive surgery, either open or laparoscopic, may take 1.5–4 h in experienced hands [240]. The anesthetic prescription should be designed to ensure tracheal extubation at the end of surgery. For the laparoscopic approach, the neonate is supine but positioned in steep Trendelenburg. All of the airway fittings should be manually tightened and IV access points extended such that they are reachable once the neonate is draped. Blood loss is usually minimal, obviating the need for blood transfusion. Caudal/epidural regional analgesia is well suited for perioperative analgesia after this surgery. Postoperatively, rectal analgesia is contraindicated.

Anorectal Anomalies

Anorectal anomalies occur in 1:4,000–1:5,000 neonates with a slight male preponderance [244]. Associated abnormalities are present in 30–60% of cases; the most common associations are listed below (Table 9.5).

Embryology

During weeks 4–6, the pouch at the caudal end of the hindgut (the cloaca) is separated into the urogenital sinus (bladder, urethra, vagina) and rectum. Anorectal anomalies occur as the result of the failure of this separation and usual subsequent degeneration (apoptosis of the membrane) resulting in a wide range of clinical abnormalities.

Classification

The Krickenbeck classification of anorectal anomalies is shown in Table 9.6 [245]. In males, imperforate anus with rectourethral fistula is the most common defect followed by rectoperineal fistulae (Fig. 9.13). In females, the most common defect is imperforate anus with rectovestibular fistula [245].

Diagnosis

Anorectal anomalies are diagnosed clinically, requiring a thorough inspection of the perineum, sacrum, and buttocks to identify the anatomy. If the neonate's clinical condition permits, it is important to wait 16–24 h after birth to diagnose a fistula, especially in males, as it may take this time for meconium to reach the rectum [246]. Associated anomalies should be sought and further investigations may be required such as an echocardiogram, abdominal X-ray, and renal ultrasound. An "invertogram" was previously advocated, but this is not routinely performed in many centers.

Outcomes

Short-term complications after reconstructive surgery include anal stenosis, which may require repeated dilatation or formal revision and wound infection. Pelvic sepsis can

Table 9.5 Conditions associated with anorectal anomalies [244]

Genitourinary (renal dysplasia, vesicoureteric reflux, undescended testes, vaginal abnormalities)
Spinosacral (sacral agenesis, vertebral anomalies, tethered cord)
Cardiac (septal defects and tetralogy of Fallot)
Gastrointestinal (esophageal atresia, intestinal atresias, Hirschsprung's disease)
Chromosomal (trisomy 21, VACTERL association, Currarino triad)

Table 9.6 Krickenbeck classification of anorectal anomalies [245]

Major clinical groups
• Perineal (cutaneous) fistula
• Rectourethral fistula (prostatic, bulbar)
• Rectovesical fistula
• Vestibular fistula
• Cloaca
• No fistula
• Anal stenosis
Rare/regional variants
• Pouch colon
• Recta atresia/stenosis
• Rectovaginal fistula
• H fistula
• Others

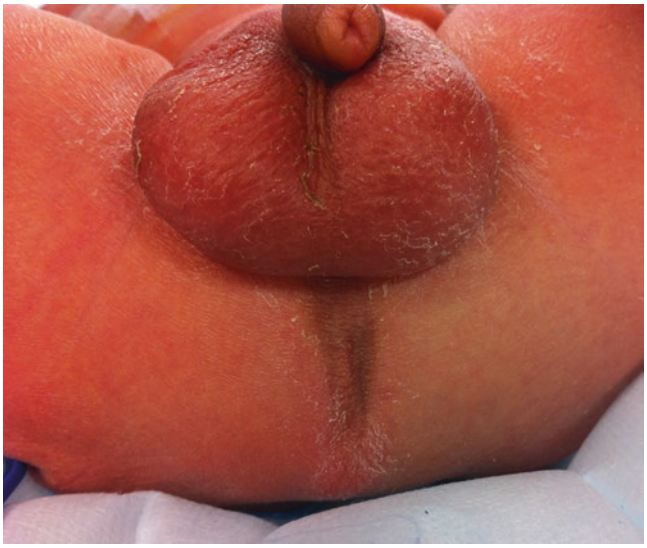

Fig. 9.13 Imperforate anus. A close-up photograph of the perineum in a male. Note that immediately inferior to the normal penis and scrotum, one observes the outline and pigmentation of the imperforate anus (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

occur as a life- and continence-threatening early complication of surgery, especially if a diverting stoma has not been performed.

Constipation is the most common long-term complication of anorectal surgery, occurring in 18–62% of infants. Fecal incontinence is a second long-term complication, occurring in 25% of infants. Social continence can often be achieved with a combination of modalities including antegrade enemas via an antegrade colonic enema (ACE) stoma. Urinary dysfunction may also occur, being attributable to the underlying urinary tract anomaly rather than the surgery.

Management

Initial management is supportive with intravenous fluids and gastric decompression with a nasogastric tube. Associated anomalies should be excluded and time allowed to detect a fistula, if clinically appropriate. Surgical decompression and reconstruction are required. Depending on the anatomy and associated anomalies, the neonate may undergo a primary anoplasty ("low" anomalies) with or without a diverting colostomy and distal mucous fistula or formation of colostomy/mucous fistula with later reconstructive surgery at 1–2 months of age ("high" anomalies). Several operative approaches have been proposed for reconstruction including posterior sagittal anorectoplasty (PSARP), an anterior sagittal approach, sacro-perineal procedure, abdomino-sacral pull-through, abdominoperineal pull-through, and laparoscopic-assisted pull-through techniques. PSARP is the most common procedure, suitable for most females and 90% of males. In the remaining males, a combined abdominal approach is required to mobilize the rectum.

Surgical Considerations

It is important to avoid damage to pelvic structures and their innervation during surgery. A muscle stimulator is essential to identify the sphincter complex and ensure correct placement of the neo-anus. For muscle function to be stimulated, muscle relaxants are avoided after induction of anesthesia. Dissection should be adequate to bring the rectum to the perineum without tension in order to minimize retraction after the repair and anal complications.

Anesthetic Considerations

An understanding of the associated anomalies, particularly cardiac and spinal anomalies, is important. Stoma formation is a relatively minor procedure in the neonatal period, and a single-shot caudal epidural provides excellent perioperative analgesia for primary anoplasty (provided there are no sacral abnormalities). Reconstructive surgery is usually performed in the prone position (PSARP) or occasionally as a combined abdominoperineal or laparoscopically assisted procedure. Intravenous access should be placed in the upper extremities to ensure that the fluids are infused into the circulation, not the surgical field. Blood transfusion is rarely required for this surgery. These reconstructive surgeries are usually several hours in duration, with the neonates in the Trendelenburg position. As a result, tracheal intubation is usually required. The anesthetic prescription should be designed to extubate the trachea at the end of surgery. Perioperative analgesia can be achieved with a continuous caudal/epidural infusion of local anesthetics (e.g., bupivacaine, ropivacaine, or chloroprocaine) [247–250] or IV morphine infusion with or without a transversus abdominis (TAP) block if central neuraxial is contraindicated [251–253].

Cloaca

This type of anorectal anomaly is uncommon, occurring in 1:50,000 live births.

Diagnosis

Careful clinical examination will reveal a single perineal opening. Further imaging studies such as contrast studies and CT scan with reconstruction can be very useful, as well as assessment of the common channel and structure via cystoscopy.

Management

Initial management is supportive as for other anorectal anomalies. Of note, hydrocolpos can result in urinary obstruction and pyocolpos can result in perforation. Both of these conditions may require urgent drainage.

Outcomes

The long-term results for cloacal repair in terms of continence are worse than for lower anorectal anomalies. Only 10% of neonates with a common channel >3 cm in length will be continent.

Surgical Considerations

Recognition of the anomaly is important as a more proximal transverse colostomy is required to allow for adequate length for the reconstruction procedure. Assessment of the length of the common channel before reconstructive surgery is important for both prognostic reasons and to assess the need for a combined intra-abdominal approach.

Abdominal Wall Defects

Gastroschisis

Gastroschisis occurs in 1:4,000 live births, affecting males and females equally, and incidence has continued to increase over the past 20 years. Gastroschisis is strongly associated with maternal age <20 years, smoking, use of recreational drugs, low maternal weight, maternal genitourinary infection, and low socioeconomic status [254–258].

Pathophysiology

Gastroschisis is usually a small, right-sided (<10% left) defect in the abdominal wall lateral to the intact umbilical cord, through which the intestines protrude, uncovered, and unprotected (Fig. 9.14). The exact embryological mechanism for this anomaly is still unclear. In utero, the eviscerated bowel floats uncovered and exposed in the amniotic fluid. This may contribute to the thickening of the bowel wall and fibrinous "peel" that is often present on the bowel at delivery. The abdominal wall defect can narrow later in pregnancy, resulting in obstruction and ischemic changes to the gut. Associated anomalies are infrequent with this defect, but when they occur, they are usually gastrointestinal in origin. For example, intestinal atresias occur in 10–15% of cases. The liver rarely herniates.

Diagnosis

The majority of neonates with gastroschisis are diagnosed on routine antenatal ultrasound. Blood testing shows increased maternal serum concentrations of alpha-fetoprotein in the absence of myelomeningocele. "Complicated gastroschisis," as in the case of gastroschisis with intestinal atresia, may be predicted by the presence of dilated bowel on antenatal ultrasound [259]. Approximately 30–70% of neonates have intrauterine growth retardation or small for gestational age. The mechanism for this latter effect is unclear but may be due to enteric loss of proteins or inadequate supply of fetal nutrients [260]. After delivery, the laterality of the defect, the absence of a sac, and an intact umbilical cord differentiate gastroschisis from omphalocele.

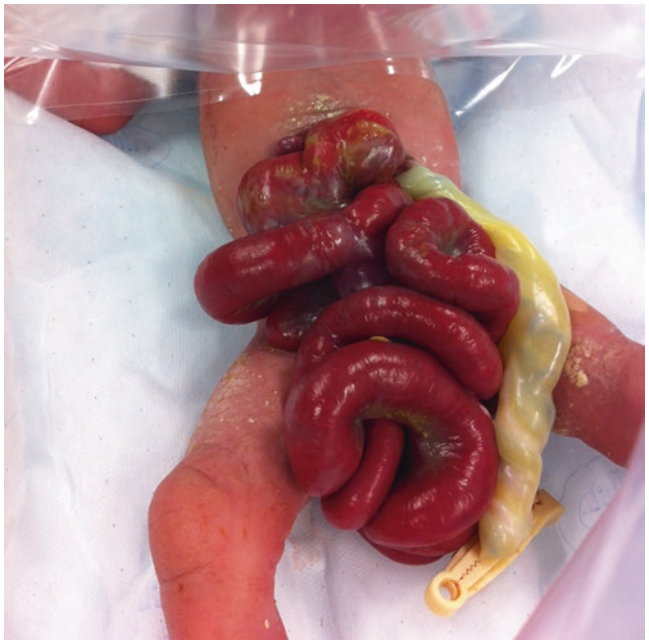

Fig. 9.14 Gastroschisis. In this preterm neonate, the thickened, red bowel from gastroschisis lays open and exposed. Note that gastroschisis arises from an anterior abdominal wall defect on the right side, lateral to the intact umbilical cord (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

Management

Antenatal diagnosis allows prenatal planning and transfer of the parturient to a center where surgical management of the gastroschisis and a level-3 nursery are available [261]. There is insufficient evidence to determine the optimal management of these fetuses, for example, the age at which the fetus should be delivered and the delivery technique [258, 262]. A survey of maternal-fetal medicine practitioners in Canada suggested that preterm (<36 weeks) delivery of fetuses with gastroschisis was associated with more complications, i.e., greater time requiring parenteral nutrition and greater length of stay in NICU, whereas delivery of fetuses ≥38 weeks was associated with increased bowel matting and a meta-analysis was unable to provide further clarity [263, 264]. There is no evidence that cesarean section improves neonatal outcomes, although early induction of labor (from gestational week 36) may avoid the unexplained late fetal deaths that can occur with this condition.

Initial management at delivery is supportive, avoiding hypothermia, hypovolemia, and sepsis. The exteriorized bowel should be wrapped in clear plastic film and supported in the midline to minimize venous engorgement or placed in a preformed silo. Above all, care must be taken to avoid damaging

the exposed bowel. A servo-controlled warm incubator should be used. Large volumes of intravenous fluids may be required to offset the large evaporative fluid loss from the exposed bowel. Broad-spectrum antibiotics should be given. A nasogastric tube should be placed to decompress the stomach and bowel.

Outcomes

Survival with gastroschisis is reported to be 90–95%, with the majority of deaths due to massive bowel resection or necrosis [265]. Intestinal function may be slow to recover after closing the defect, necessitating a long period of parenteral nutrition. A review of a gastroschisis database indicated that the time to achieve independence from parenteral nutrition, reduce the length of stay, and achieve freedom from infection was optimized when enteral feeds were withheld for at least 7 days after closure of the defect [266]. However, these findings should be interpreted in the context of the neonate's status. Intestinal dysfunction and short bowel syndrome complicate gastroschisis. Gastroschisis accounts for approximately 20% of the cases of short bowel syndrome, with the incidence of the latter inversely proportional to birth weight [267]. Surgical short bowel syndrome is defined as the need for parenteral nutrition for >3 months. Current advances in management strategies that involve a multidisciplinary team approach, parenteral nutrition, prophylaxis from infection, and ongoing surgical consultation have dramatically improved bowel function and survival in these neonates [267, 268].

Surgical Considerations

The primary objective of surgery is to cover and protect the bowel. The secondary objective is to effect a staged return of the bowels to the abdomen, without causing an abdominal compartment syndrome. The latter is often identified by the onset of respiratory distress, ischemic or necrotic bowel, and renal insufficiency. For monitoring strategies to identify abdominal compartment syndrome, see Anesthetic Considerations below.

The surgical treatment of gastroschisis remains controversial. Primary closure may be undertaken in neonates with small-size gastroschises using general anesthesia in the operating theater. Complications such as intestinal atresia, perforation, necrosis, or volvulus may be addressed at the same time. Before attempting a primary closure, rectal decompression with possible rectal washouts may decrease intraluminal contents and facilitate a smooth reduction. Good long-term outcomes have also been reported using a "sutureless ward reduction" protocol with morphine sedation for carefully selected neonates with uncomplicated gastroschisis. The bowel is inspected carefully for intestinal anomalies and the neonate remains conscious during the procedure. The reduction should be abandoned if the neonate develops respiratory distress or the surgeon perceives the abdominal pressure is excessive [269].

A staged closure is required if primary closure is not appropriate or possible. A hand-sewn Prolene mesh silo is applied surgically under general anesthesia or using a preformed spring-loaded silo. For neonates with uncomplicated gastroschisis who do not have significant viscero-abdominal disproportion, the preformed silo can be applied in the neonatal unit without the need for general anesthesia or tracheal intubation [270]. These techniques allow gradual compression of the bowel into the abdomen over a period of days and facilitate early extubation. The neonate undergoes planned surgical closure 3–5 days later, or closure of the defect using adhesive strips once the bowel is fully reduced, depending on the silo technique used [270]. The use of the preformed silo may be associated with reduced ventilator days in the NICU, but this approach may also be associated with specific technical complications that could lead to venous congestion of the intestine resulting in bowel ischemia [271].

Anesthetic Considerations

Some centers do not use anesthesia for closure of gastroschisis if a sutureless or preformed silo technique is used, although others recommend routine anesthesia with paralysis to facilitate every attempt to reduce the bowel. An operative technique is required for complicated gastroschisis. A combination of general anesthesia with epidural anesthesia provides good postoperative analgesia and may reduce the need for postoperative ventilation [272]. The child must be kept warm and well hydrated with fluid blouses of 20 mL/kg Ringer's or albumin. Arterial access is useful for monitoring complex procedures. In neonates with otherwise uncomplicated gastroschisis, enteral feeding usually begins 7–10 days after delivery. In those who require long-term parenteral nutrition, it is important to preserve veins for chronic catheters for long-term parenteral feeding. Some units advocate placement of a tunneled feeding line at the time of initial surgery [273].

The major concern that may arise during closure is the development of abdominal compartment syndrome. If the reduction is performed under general anesthesia, care should be taken during face mask ventilation to minimize the peak inspiratory pressure to avoid gaseous distention of the stomach and small intestine, and nitrous oxide should be avoided. Intra-abdominal pressures should be maintained <20 mmHg during primary closure of the defect; otherwise, excess pressure may limit venous return and/or bowel and renal vascular insufficiency [274]. Some centers use a balloon-tipped catheter in the bladder or stomach, central venous pressure, or $P_{ET}CO_2$ to track serial changes in intra-abdominal pressure during closure [275, 276]. If the intragastric pressure >20 cm H_2O or the $P_{ET}CO_2$ >50 mmHg the attempted closure, then primary closure should be halted and a staged closure considered—similarly, if the ventilator settings should be noted at the start of the procedure and followed throughout to iden-

tify any decreases in tidal volume due to upward movement and splinting of the diaphragm. During closure, the bowel must be constantly assessed for signs of venous congestion. Urine output can be used to reflect the adequacy of renal perfusion after completing the surgery. After closure but before leaving the operating room, the lower limbs should be examined for evidence of venous compromise and pulses.

Exomphalos (Omphalocele)

Exomphalos occurs in 1:4000 live births, affecting males 1.5 times more frequently than females. It can be classified as major, minor, or giant, depending on the size of the defect and the presence of liver herniation. Major defects are greater than 4 cm in diameter or contain a herniated liver. Giant defects are greater than 6 cm in diameter or contain a herniated liver. Associated anomalies are common, occurring in more than 50% of neonates, particularly those with a minor defect. Anomalies associated with exomphalos include chromosomal abnormalities (30%) such as trisomies 13, 18, and 21, other midline defects (pentalogy of Cantrell, bladder and cloacal anomalies), and cardiac and musculoskeletal abnormalities. Beckwith-Wiedemann syndrome, an abnormality found on chromosome 11 associated with gigantism, macroglossia, exomphalos, pancreatic islet cell hyperplasia with hyperinsulinism, organomegaly, and hemihypertrophy, occurs in 12% of cases. Pulmonary hypoplasia is associated with exomphalos major.

Pathophysiology

Exomphalos is a central defect of the umbilical ring. The herniated organs are covered with a membrane (sac) continuous with the umbilical cord (Fig. 9.15). This is thought to represent the failure of the intestines to retract into the abdominal cavity from the umbilical stalk after the period of rapid growth of the intestines early in embryogenesis.

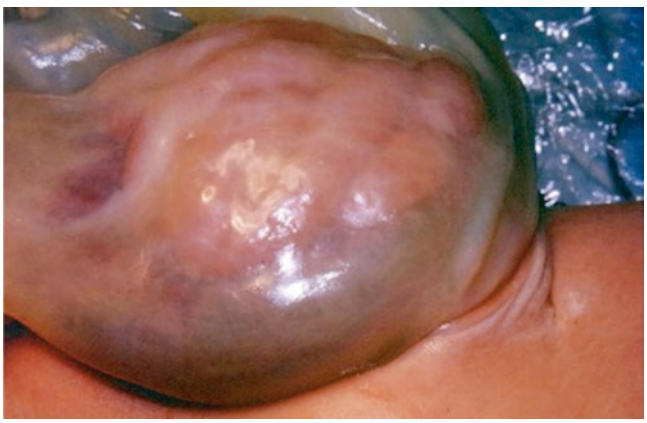

Fig. 9.15 Omphalocele. In this midline defect, the herniated bowels are covered by a thick membrane (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

Diagnosis

As in gastroschisis, the diagnosis of exomphalos is confirmed antenatally using ultrasound imaging. Exomphalos is a midline abdominal wall defect with a sac that contains the herniated visceral contents. Antenatal chromosome testing is recommended. After delivery, the defect in the umbilical ring is visible, usually with an intact sac. It can be difficult to visualize externally whether the liver is herniated.

Outcomes

The mortality rate in neonates with exomphalos, 10–30%, is substantively worse than it is for gastroschisis. However, unlike gastroschisis in which the severity of the bowel dysfunction and ischemia determines the morbidity and mortality in that condition, the severity of the associated anomalies determines the morbidity and mortality in exomphalos. There is increasing recognition of the pulmonary complications in exomphalos especially exomphalos major or giant exomphalos due to as-yet-unexplained pulmonary hypoplasia or pulmonary hypertension [277].

Management

Supportive management is the initial priority. If the sac remains intact, then the bowels are protected and urgent surgical intervention is unnecessary. The sac and its contents should be supported depending on its size. Time can be taken to delineate and stabilize the associated anomalies before proceeding with reduction. If the sac has ruptured, then surgical intervention becomes more urgent as in the case of gastroschisis.

Surgical Considerations

Primary reduction of the contents with excision of sac is usually achievable for small defects, but a staged closure is generally required for larger defects. A hand-sewn surgical silo is placed under general anesthesia, leaving the sac intact, with serial reductions performed in the neonatal unit, including after extubation. Once the visceral contents have been reduced, the silo can be removed and the defect formally closed in theater. The likely success of primary closure should be assessed by gentle compression before excising the sac. If not favorable, then the sac should be left intact for silo placement. If the sac is excised, care must be taken superiorly to avoid damaging the hepatic veins, which may cause a significant hemorrhage. Neonates with giant exomphalos are occasionally treated conservatively, particularly if there is marked disproportion between the viscera and the size of the abdominal cavity (typical "scaphoid" abdomen). The intact sac is allowed to epithelialize, with topical application of antibacterial sclerosing agents such as povidone-iodine or silver sulfadiazine, although systemic absorption of iodine or silver may themselves create a problem [278].

Anesthetic Considerations

The preoperative assessment should include an echocardiogram and appropriate investigations to fully define the severity of any other anomalies present. Otherwise, the anesthetic prescription is similar to that for gastroschisis repair. Neonates with exomphalos major are particularly at risk for abdominal compartment syndrome. Reduction of the liver into the abdomen can compress the inferior vena cava, acutely decreasing venous return and cardiac output. Intra-abdominal pressure can be monitored using either a bladder or gastric pressure transducer (see above) to provide an objective metric upon which to stage the reduction. As in gastroschisis, close and clear communication between the surgeon and anesthesiologist will ensure a successful reduction.

Bladder Exstrophy/Cloacal Exstrophy

Bladder exstrophy occurs in 1:30–50,000 live births affecting males four times more frequently than females. Antenatal diagnosis occurs in only 25% of cases [279]. This defect in the anterior bladder and abdominal wall exposes the bladder and urethra as part of the exstrophy-epispadias complex (Fig. 9.16).

Cloacal exstrophy occurs four to five times less frequently than bladder exstrophy, in 1:200,000 live births. It occurs equally in both males and females. Cloacal exstrophy is a lower abdominal wall defect with two hemibladders separated by a midline cecum, exomphalos, and imperforate anus. Spinal malformations such as myelomeningocele may occur as part of the omphalocele-exstrophy-imperforate anus-spinal defect (OEIS) complex.

Outcomes

Optimal outcomes for these rare conditions are obtained by centralizing the care to specialist centers, with the involvement of a multidisciplinary team. Previously a commonly fatal condition, the dramatic advances in neonatal care have transformed the outcome from this defect to almost 100% survival beyond the neonatal period, although long-term issues relating to the function and psychological outcomes remain.

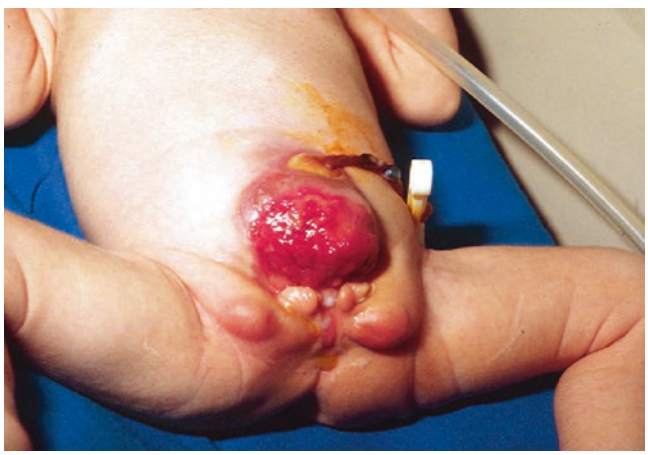

Fig. 9.16 Bladder exstrophy. This congenital defect in the anterior abdominal wall reveals the bladder wall, malformed genitalia, and widened pelvis with an absent symphysis pubis (Courtesy of Dr. RJ. Banchs, Children's Hospital, University of Illinois. Chicago, Ill)

Management

After delivery, care should be taken to avoid damage to the bladder plate. Moist nonadherent dressings should be applied before transfer of the child to the specialist center, and the umbilicus tied rather than clamped. In cloacal exstrophy, exomphalos is managed using the techniques described above.

Surgical Considerations

The long-term aims of surgery are the reconstruction of the bladder for social urinary continence, treatment of vesicoureteric reflux, reconstruction of the genitalia to allow for cosmetic appearance, sexual and urinary function, and, in the case of cloacal exstrophy, reconstruction to obtain fecal continence. As a result of the wide diastasis of the pubic bones, pelvic osteotomies are often required in order to close the pelvic brim anteriorly and reduce the risk of wound dehiscence and bladder prolapse.

Surgery may be performed in staged procedures: the bladder is closed early in the neonatal period with or without pelvic osteotomies, depending on surgical preference; the genitalia is repaired at 3–6 months of age, in some centers with a radical bladder neck reconstruction at this stage (Kelly procedure) and a secondary hypospadias procedure at 3 years; and finally, bladder augmentation and ureteric reimplantation are performed if required in later childhood. If the bladder closure and osteotomies are performed in a single procedure, a multidisciplinary approach involving anesthesia, urology, and orthopedics is the prescription for success. In this case, the anticipated duration of surgery will be quite prolonged (see below). A single-stage procedure of bladder closure, bladder neck reconstruction, and epispadias repair in the neonatal period has been described (Mitchell procedure), although concerns that urethral blood flow may be compromised with this technique must be considered [280]. The complication rate after single-stage repair is reportedly similar to those after a staged repair, although soft tissue defects may be more common in the former [281].

Anesthetic Considerations

Neonates with bladder exstrophy are usually born at term without other associated anomalies. Surgery for primary bladder closure is ideally performed in the first few days of life, while the pelvic bones remain malleable. Blood loss is significant if pelvic osteotomies are performed, and a blood transfusion is often required. A plaster cast or external fix-

ator may be applied at the end of surgery for support. Although systolic blood pressure remains a reliable metric for detecting hypovolemia in neonates, central venous access may be a useful adjunct measure to monitor fluid status during this surgery as urine output is not easily quantified. Intravenous access should be placed in the upper extremities (or neck) to retain access to the lines and to ensure that all fluids remain in the circulation. With the prolonged duration of surgery and the need to monitor blood pressure, perform laboratory tests (hemoglobin, electrolyte, and glucose concentrations), and respond to sudden blood loss, arterial access should be considered. Surgery may be prolonged (4–6 h or greater). A combination of general anesthesia and epidural anesthesia allows many neonates to be extubated at the end of surgery. Some units advocate the use of tunneled epidural catheters to facilitate immobilization and reduce wound complications [282].

Posterior Urethral Valves

Posterior urethral valves (PUV) are the most common cause of lower urinary obstruction in males, occurring more commonly in non-Caucasians at a rate of 1:5000 live births. Other less common causes of lower urinary obstruction include prune-belly syndrome and urethral stenosis or atresia. PUV are usually an isolated finding that causes severe obstructive uropathy, with 20–60% of these neonates developing chronic kidney disease in childhood and 11–51% progressing to end-stage renal failure in their lifetime [283]. Severe obstruction and oligohydramnios during lung development (16–24 weeks' gestation) may cause pulmonary hypoplasia leading to substantial fetal and perinatal mortality (33–75%) [284].

Diagnosis

PUV are frequently identified from the appearance of bilateral hydronephrosis during routine antenatal ultrasound (accounting for 10% of cases of antenatal hydronephrosis), although many do not present until later in childhood, with urinary tract infection, failure to thrive, or continence. Late diagnosis is associated with less severe renal impairment and a better long-term prognosis. At birth, renal ultrasound demonstrates a thick-walled bladder and hydronephrosis and provides an assessment of the degree of renal cortical damage. The urethral valves can be demonstrated in a voiding cystourethrogram or directly at cystoscopy.

Management

The definitive treatment for PUV in neonates is the relief of the obstruction by catheterization and antibiotic prophylaxis, with cystoscopy and transurethral ablation. The results of antenatal treatment with vesicoamniotic shunt have been disappointing to date. Long-term follow-up is required, with active management of bladder dysfunction and reflux.

Anesthetic Considerations

Cystoscopy and resection of PUV during the neonatal period is a minor procedure that requires a brief general anesthetic. Nonetheless, most prefer to secure the airway in these neonates with a tracheal tube (rather than a supraglottic device) because the neonate may be positioned either cross-table or at the end of the operating room table and the duration of surgery is somewhat unpredictable, dependent on the extent of the pathology. Significant comorbidities such as pulmonary hypoplasia and renal dysfunction must be considered when planning the anesthetic prescription. Antibiotic prophylaxis is essential. A single-shot caudal epidural block can provide excellent perioperative analgesia depending on the extent of the surgery.

Sacrococcygeal Teratoma

Sacrococcygeal teratoma occurs in 1–2:40,000 live births, representing 35–60% of all teratomas [285]. Females are more commonly affected than males by a 3–4:1 margin (Fig. 9.17). These tumors arise from an embryonic cell line in the pelvis that contains cells in different proportions from the ectoderm, mesoderm, and endoderm [286]. Structurally, sacrococcygeal teratomas are classified as cystic, solid, or a combination of the two. Cystic teratomas comprise 15% of all sacrococcygeal teratomas, have more differentiated cells, and are usually benign. The majority of sacrococcygeal teratomas are solid or mixed (Fig. 9.18). The more solid the composition of the teratoma, the more likely it is to be malignant.

Perinatal mortality in neonates, whose tumors are diagnosed antenatally, is 25–37%. Mortality is more likely in fetuses with rapidly growing vascular teratomas that act

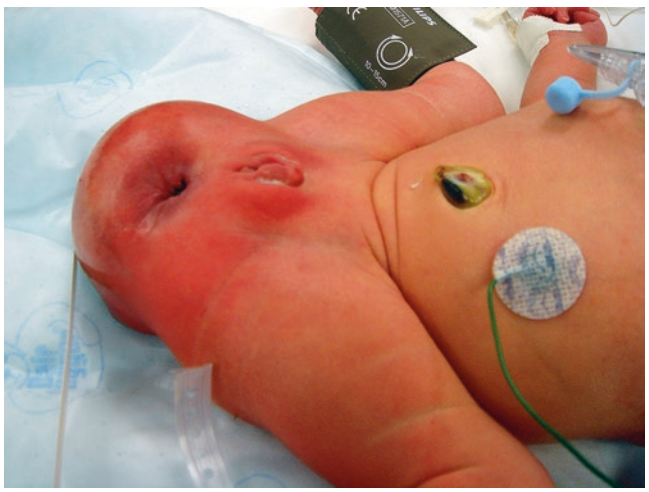

Fig. 9.17 Sacrococcygeal teratoma. This tumor was located on the outside of the sacrum, completely external to the pelvis. Consistent with the greater incidence of sacrococcygeal teratomas in females, this neonate was a female (Courtesy of Dr. W. Pegoli, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

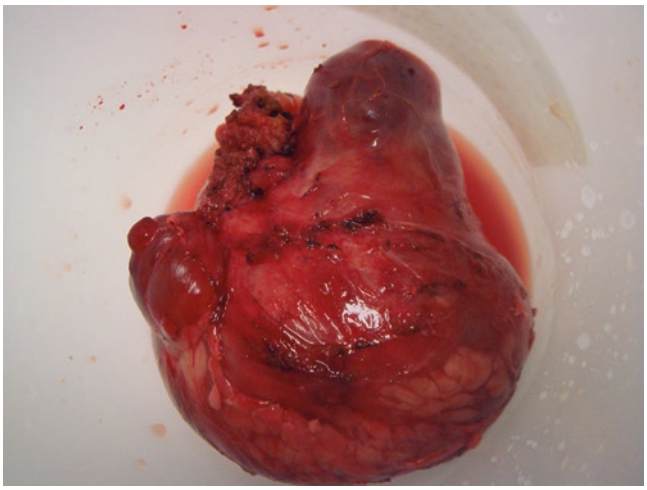

Fig. 9.18 Excised sacrococcygeal teratoma. The tumor appears to be multiloculated, but mostly solid in this case

physiologically as arteriovenous malformations. These malformations lead to hydrops, polyhydramnios, high-output cardiac failure, preterm birth, and death. Two variables suggest a greater risk for a poor prognosis: the ratio of the tumor volume to the fetal weight >0.11 determined before 32 weeks' gestation and tumor morphology <60% cystic [287, 288].

At delivery, 90% of sacrococcygeal teratomas are benign; the minority is malignant. However, the malignancy rate increases dramatically from 10% at birth to 75% by 1 year of age and 100% by 5 years of age if the tumor is not resected. Hence, early detection and antenatal intervention or surgical excision of the tumor at birth is crucial to achieving long-term survival.

The Currarino triad, which is comprised of a presacral tumor, anorectal malformation, and sacral anomaly, follows an autosomal dominant familial inheritance pattern from a genetic defect on chromosome 7. Urogenital anomalies have been identified in females with sacrococcygeal teratomas and should be suspected in any female with voiding difficulties [289].

Diagnosis

Sacrococcygeal teratomas are often detected antenatally using ultrasound. Differential diagnoses include meningocele, lymphangioma, lipoma, or taillike remnant. At delivery, 85–95% of these teratomas are external midline sacral masses. The skin covering the mass is usually normal, although hemangiomas, ulcers, and evidence of necrosis may be present [285]. Investigations should be performed preoperatively to define the borders of the mass within the pelvis. In older children, the tumor may be entirely intrapelvic, without external evidence of the tumor. The Altman classification of sacrococcygeal tumors is based on the postnatal assessment of the external and internal elements of the teratomas (Table 9.7) [290].

Table 9.7 The Altman classification of sacrococcygeal tumors [290]

Type 1—tumor is predominantly external with minimal presacral component
Type II—tumor presents externally, but with substantial intrapelvic extension
Type III—tumor is present externally, but the bulk of the tumor is intrapelvic with extension into the abdomen
Type IV—presacral tumor with no external component

Management

Complications associated with sacrococcygeal tumors relate to their vascularity, size, and position. In utero, the fetus should be monitored for the development of hydrops and placentomegaly. These occur in rapidly growing vascular teratomas that cause a vascular steal syndrome, which in turn may precipitate high-output cardiac failure necessitating an urgent in utero intervention to prevent premature delivery and/or death. These interventions may include amnioreduction, cyst aspiration, radiofrequency ablation, shunts, and surgical debulking [291, 292]. Outcomes after in utero interventions are similar to those who did not undergo interventions, despite the worsened features present in the intervention group, with a mortality between 25% and 45% [292, 293]. Cesarean section is indicated for large tumors, that is, for those larger than the neonate's biparietal diameter [285]. Vaginal deliveries are best avoided in neonates with large tumors as the latter may rupture causing the neonate to rapidly exsanguinate. Rectal examination should be performed with great care to avoid rupturing the tumor. Imaging techniques including abdominal X-ray, echocardiogram, ultrasound, and/or MRI will help to define the anatomy, location, and vascularity of the tumor. Tumor markers should be monitored (alpha-fetoprotein and beta-HCG): alpha-fetoprotein increases in the presence of a malignancy. These should be followed postoperatively to detect a malignant recurrence.

Outcomes

If the sacrococcygeal teratoma is identified as an incidental finding during the antenatal period, the expected survival rate is 90%. Mortality approaches 60% in complicated pregnancies and 100% in the presence of hydrops or placentomegaly, which reflects high-output heart failure due to shunting through the vascular teratoma.

The prognosis in terms of malignancy depends on the tumor type, stage, location (Altman classification), and completeness of excision, in addition to the child's age at the time of the operation. If the initial resection is performed after the neonatal period, the risk of a recurrence increases substantially, especially if the serum alpha-fetoprotein concentration is increased. Up to 7% of tumors recur, mostly

within the first 3 years. These tumors recur locally, although metastases are possible. The long-term prognosis in these children, including those with a malignant sacrococcygeal teratoma, exceeds 80% due to platinum-based multimodal chemotherapy [285].

Poor functional outcomes are becoming increasingly recognized with an increased rate of urological and bowel functional issues being identified in >50% of patients. Patients require focused follow-up in this regard and it is not clear whether this represents a tumor or surgery effect [291, 294, 295].

Surgical Considerations

Once the airway is secured, monitoring and vascular access (including arterial access) are established, and the bladder is catheterized, the neonate is turned prone (Fig. 9.19a, b). The coccyx should be removed with the tumor for complete excision of the tumor. If the tumor has a small intrapelvic component, it should be resectable in this position. A combined posterior and abdominal approach may be indicated for larger intrapelvic tumors or in cases where early vascular control is required. Bleeding is the major risk for this condition and preoperative IR embolization has been advocated in some instances.

Anesthetic Considerations

Excision of sacrococcygeal teratoma is a high-risk procedure, with significant perioperative morbidity and mortality. In some cases, it may be prudent to have two experienced anesthesiologists to provide anesthesia for these cases as sacrococcygeal teratomas have been known to hemorrhage suddenly and massively. The perioperative risks relate primarily to a major hemorrhage from the highly vascular tumor, in the context of a neonate who may be premature and have pulmonary hypertension, renal and hepatic impairment, and a coagulopathy associated with high-output cardiac failure. Access to the neonate may be compromised if surgery is performed in the prone position. It is essential to make preparations for major blood loss with crossmatched fresh blood and blood products. Intraoperative cardiac arrest has been reported from hyperkalemia and hypocalcemia associated with a rapid, massive transfusion, especially when transfused rapidly through a central venous catheter, and hyperkalemia has been associated with surgical manipulation of a necrotic tumor [296]. Fresh pRBC is preferable and should be transfused slowly after warming, preferably through a peripheral IV rather than a central line. Activation of the major hemorrhage protocol or massive transfusion protocol for neonates enables a balanced coordinated approach to a major blood loss. Several protocols have been published with proposed massive transfusion protocols in pediatrics (according to the infant's weight) including the Starship Massive Transfusion protocol from Auckland, New Zealand (https://www.starship.org.nz/guidelines/massive-transfusion-protocol/, Accessed April 4, 2021) although these protocols are only empirical [297–299].

At the conclusion of surgery, the neonate should be transferred to the intensive care unit in the prone position. The bladder catheter remains in situ for 24 h. The serum concentration of alpha-fetoprotein should be monitored on a regular basis to assess the risk of a malignant recurrence.

Biliary Atresia

Biliary atresia (BA) is the progressive obliteration and sclerosis of the extra- and intrahepatic bile ducts leading to liver fibrosis, cirrhosis, and death if untreated, occur-

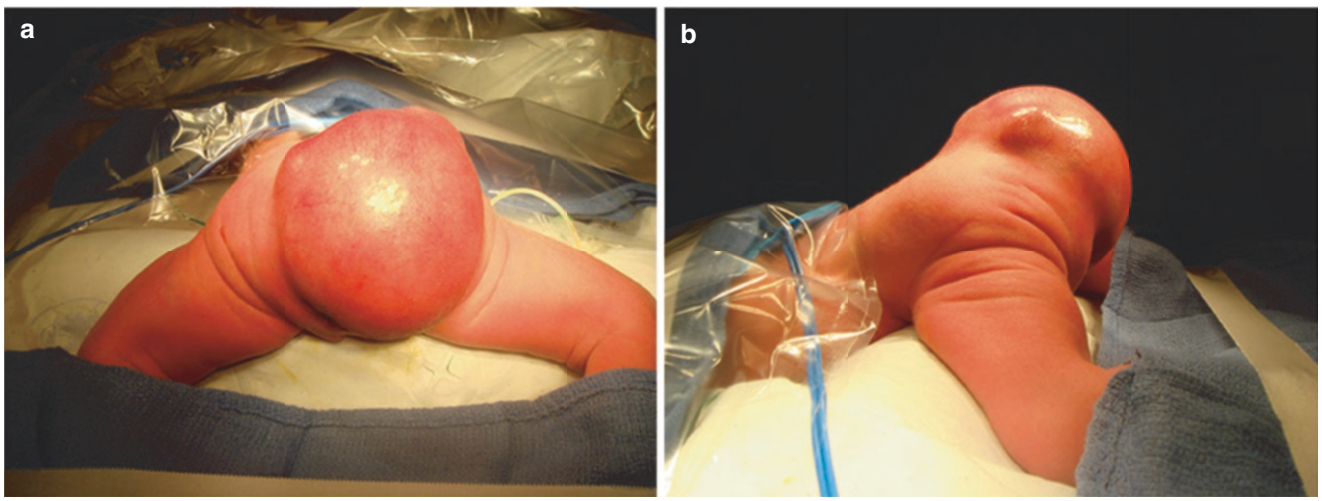

Fig. 9.19 Sacrococcygeal teratoma. (**a**) Caudal view. (**b**) Lateral view. The neonate was anesthetized, the tracheal intubated, and the neonate positioned prone for surgery. Note the large size of the tumor relative to the neonate (Courtesy of Dr. W. Pegoli, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

ring in 1:10,000–15,000 live births. Its etiology is unknown; however, environmental and genetic/developmental aspects have been proposed [300]. It is associated with other anomalies in 15–20% of cases. Biliary atresia splenic malformation syndrome (BASM) occurs in 10% of cases, with polysplenia or asplenia, cardiac abnormalities, situs inversus, malrotation, preduodenal portal vein, and absent vena cava [301].

Classification

BA is classified according to the level of obstruction of the extrahepatic bile ducts (Table 9.8). Type III is further subdivided according to the pattern of obstruction of the common bile duct (CBD) and distal ducts. The most common type of BA is type IIIb.

Diagnosis

The key feature of BA is prolonged jaundice (conjugated hyperbilirubinemia) beyond the first 2 weeks of life with signs of biliary obstruction (pale stools and dark urine), in an otherwise healthy term neonate [301]. Infants who present later may show signs of failure to thrive due to fat malabsorption, with coagulopathy due to failure to absorb vitamin K, hepatosplenomegaly, and ascites [302]. The initial meconium is usually colored, as obstructive jaundice develops postnatally. Diagnosis of BA is usually made by liver biopsy or occasionally laparoscopic cholangiogram with the direct puncture of the gall bladder, or radioisotope scan to detect bile acid in the intestine (hepatobiliary iminodiacetic acid (HIDA) scan) [301, 303].

The differential diagnosis of BA includes the choledocal cyst, inspissated bile syndrome, and other infective/metabolic causes of neonatal hepatitis, which should be excluded with a TORCH screen, metabolic screen, and ultrasound. Choledocal cyst is a cystic disorder of unknown etiology affecting the pancreatobiliary system. Children may present with jaundice and an abdominal mass at any age from birth to adulthood. Without treatment, this disorder may progress to cholangitis or cirrhosis. The anesthetic considerations are similar to BA, although the underlying hepatic function is usually normal, apart from obstructive jaundice.

Table 9.8 Classification of biliary atresia

Type I—obstruction at common bile duct (5% of cases)
Type II—obstruction at the common hepatic duct (2% of cases)
Type III—obstruction of the porta hepatis (>90% of cases)
Subtype a. Patent CBD, atrophic gall bladder
Subtype b. Fibrous CBD, atrophic gall bladder
Subtype c. Absent common hepatic duct, mucocele of gall bladder
Subtype d. Miscellaneous

Management

Once the diagnosis has been made, any coagulopathy should be corrected and surgery planned. Being a rare condition, best outcomes are usually obtained when these neonates are referred to a specialist center. In the UK, children with BA should be referred to one of three national specialist centers. Long-term prognosis is linked to the timing of operative correction of bile flow, so ideally, surgery should be performed as soon as possible, usually at age 1–2 months. Jaundice usually clears early in 50–60% of patients. These children have a good 5-year prognosis, although liver transplantation may be required for those with persistent jaundice or clinically significant portal hypertension. Long-term survival is expected in 90% of cases, although neonates may have significant long-term morbidity that is related to hepatic cirrhosis or the effects of immunosuppression after liver transplantation.

Surgical Approach

The initial surgery consists of an open Kasai procedure. Laparoscopic techniques do not appear to offer advantages such as fewer adhesions, over the open approach [304–308]. The Kasai procedure involves resection of the extrahepatic biliary tree including the portal plate and the fashioning of a Roux-en-Y jejunal anastomosis at this level to restore bile flow to the intestinal tract. If the diagnosis is not clear before the laparotomy, then an intraoperative cholangiogram can be performed before dissection [301]. Factors that predict success after a Kasai procedure include preoperative direct bilirubin <2, absence of liver fibrosis, and limited episodes of cholangitis [302].

Anesthetic Considerations

Coagulopathy should be corrected preoperatively using vitamin K. Platelets and fresh frozen plasma may occasionally be required as well. Oral neomycin and clear fluids should be given for 24 h preoperatively. Broad-spectrum prophylactic antibiotics are essential before skin incision and for 5 days postoperatively to prevent cholangitis (e.g., gentamicin and cefoxitin). Isotonic maintenance fluids containing dextrose are required to avoid intraoperative hypoglycemia, e.g., 1–5% dextrose in lactated Ringer's solution or 5% dextrose in PlasmaLyte. Transfusion is usual, although massive blood loss is uncommon. Hepatorenal syndrome has not been reported in this age group. Ascites is uncommon, but if it develops, losses should be replaced with 5% albumin. Active warming and invasive access are required as surgery usually takes 2–4 h. An opioid-based/muscle relaxant technique is ideal, avoiding nitrous oxide to prevent bowel distension. The surgeon may kink the inferior vena cava during mobilization of the liver resulting in unexpected hypotension, which may require the immediate infusion of additional intravenous flu-

ids or vasopressor infusion to maintain circulatory homeostasis. At the end of the surgery, the tracheas of most neonates can be extubated. These neonates are best managed in a high-dependency unit with morphine analgesia [309].

Necrotizing Enterocolitis

Necrotizing enterocolitis (NEC) is the most common surgical neonatal emergency affecting up to 0.5% of all live births and 10% of low-birth-weight (<1500 g) live births [310]. The overall incidence of NEC, both medical and surgical, appears to be steadily decreasing, along with the mortality rates [311]. Advances in neonatal care have improved survival rates for premature and low-birth-weight infants, as well as those affected by this disease.

Pathogenesis

The etiology of NEC remains unclear although risk factors include prematurity, early formula feeding, cardiac disease, low birth weight, transfusion in the preceding 48 h (transfusion-associated NEC), and sepsis [312, 313]. Breast milk appears to be protective, likely due to transferred immunoglobulins. Multiple gut factors predispose to the development of NEC in preterm neonates including dysmotility, abnormal microbiota, reduced mucin barrier, increased gut permeability, decreased immunoglobulins and gut immunity, increased risk of ischemia, and slow gastric emptying [314, 315]. This in turn may facilitate bacterial translocation across the bowel wall triggering an inflammatory cascade that results in ischemic damage to the bowel. The pathological organisms are often endogenous bowel flora, suggesting an imbalance in the defensive mechanisms rather than a specific virulent organism, although clusters of cases have been known to occur.

Diagnosis

NEC is primarily a clinical diagnosis [310]. It is classified according to the criteria described by Bell (Table 9.9) [316].

Table 9.9 Bell classification for diagnosing NEC [316]

Stage IA—suspected disease: temperature instability, increased aspirates, mild distension; radiology normal or dilated loops
Stage IB—as above, with bright red blood per rectum
Stage IIA—proven NEC, mildly ill: as above with absent bowel sounds, ± abdominal tenderness; radiology shows intestinal dilatation, ileus, pneumatosis intestinalis
Stage IIB—proven NEC, moderately ill: mild metabolic acidosis, mild thrombocytopenia, absent bowel sounds, abdominal tenderness +/− redness of abdominal wall or abdominal mass; radiology shows portal vein gas +/− ascites
Stage IIIA—advanced NEC, severely ill: as above with hypotension, bradycardia, metabolic acidosis, disseminated intravascular coagulation, neutropenia, generalized peritonitis, tenderness and distension; radiology as above with definite ascites
Stage IIIB—advanced NEC, severely ill with perforation: as above with pneumoperitoneum on abdominal X-ray

Early signs include feeding intolerance, bilious vomiting or increased nasogastric aspirates, abdominal distension with or without tenderness, hemodynamic instability, and blood per rectum (Fig. 9.20). Thrombocytopenia, coagulation abnormalities, and increased inflammatory markers such as C-reactive protein are common. Radiological investigations are often helpful in confirming the presence of NEC. Pathognomonic findings of NEC on abdominal X-ray include distended loops of bowel, pneumatosis intestinalis, and portal venous gas with or without free perforation (Fig. 9.21). The value of ultrasound and other imaging modalities as diagnostic or prognostic tests has yet to be established; however, US may be a useful adjunct [317]. Recent laboratory investigations have identified several biomarkers that herald the onset of NEC/sepsis [318, 319]. Such insights may provide the basis for future studies to identify biomarkers that will identify a neonate's risk of developing NEC.

Outcomes

Despite early and aggressive therapy and support, the mortality from NEC remains substantial, in our local series rang-

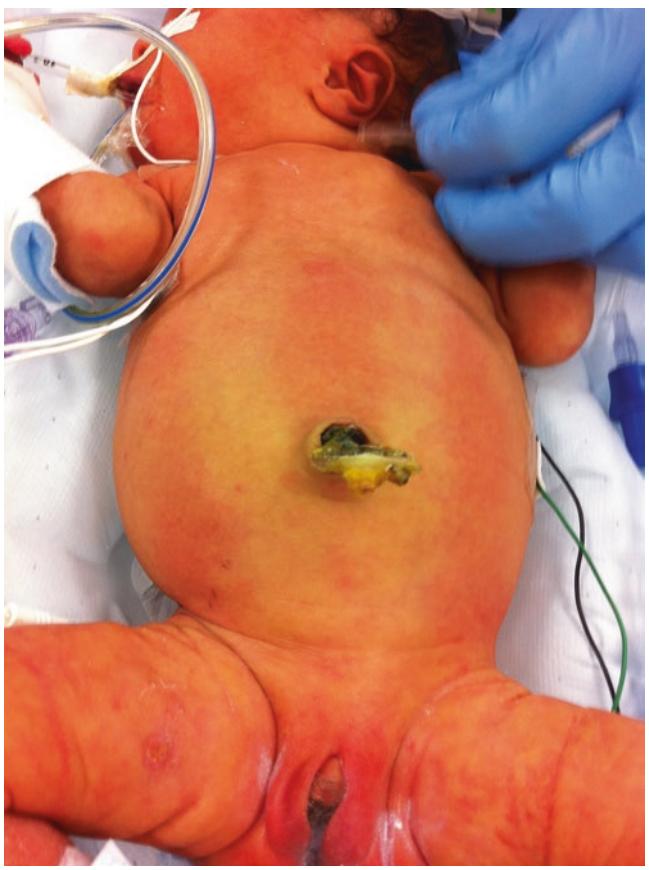

Fig. 9.20 NEC in a premature neonate. This neonate developed NEC and a distended abdomen. Note the "rectus muscle-sparing" lines separated from the erythema of the anterior abdominal wall (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

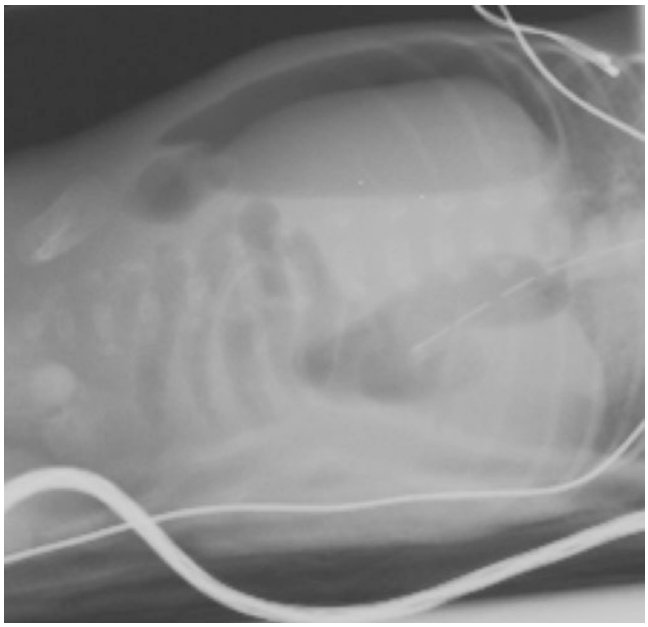

Fig. 9.21 Lateral radiograph of a neonate with NEC. The neonate was positioned in the left lateral decubitus position with a multi-orifice gastric tube in the stomach. Free air is evident against the right (*upper*) lateral abdominal wall, outlining the liver and falciform ligament (Courtesy of Dr. YH Lee, Division of Pediatric Surgery, Strong Hospital, University of Rochester, Rochester, NY)

ing from 30% to 90% with pan-intestinal disease [320]. In a large prospective study, perioperative mortality was 30% for all neonates with NEC, compared with 6% in those managed medically [320, 321]. The mortality rate in neonates who were treated with primary peritoneal drainage alone was 50%. A multicenter retrospective review between 2006 and 2017 in the USA suggested mortality from NEC has been steadily decreasing along with the incidence of NEC, as well as the mortality from any primary peritoneal drainage, now at 35% [311]. Significant morbidity occurs in up to 25% of operative neonates, including stricture formation and failure to thrive, and in those who require extensive resection, short bowel syndrome, and long-term requirement for parenteral nutrition with the associated risk of liver disease and sepsis [322]. Neonates with NEC may also experience worse neurological outcomes, particularly those with advanced disease that require surgical intervention [323]. A recent review has confirmed poor outcomes including high mortality supporting ongoing research into this condition [324].

Management

The primary approach to NEC is to adopt strategies that prevent the disorder. Such strategies include standardized enteral feeding, exclusive use of human breast milk and milk-based fortifiers, minimal antibiotic exposure, minimal gastric acid blockade therapy, and the use of high-quality probiotics, if the preceding measures fail [314, 325–328].

Definitive studies for managing NEC once it has occurred are lacking, and treatment has been determined by expert consensus and the neonate's clinical condition [329]. The first-line treatment is medical, targeting sepsis and preventing further intestinal damage. The neonate is kept nil by mouth for 7–10 days, with a nasogastric tube in situ to decompress the stomach, intravenous broad-spectrum antibiotics, and appropriate cardiorespiratory and hematological support. Nutritional challenges can be addressed using total parenteral nutrition (TPN).

It is important to appreciate a little known risk of red cell hemolysis when considering to transfuse with fresh frozen plasma or blood products with plasma [330]. The T antigen, also known as the Thomsen-Friedenreich (or T) cryptantigen, is a naturally occurring but concealed red cell antigen (cryptantigen) that becomes activated when bacteria (e.g., streptococcus, pneumococcus, and *Clostridium perfringens*) carrying neuraminidase activate the T antigen. Transfusion of plasma that contains immunoglobulin M anti-T antigen binds this activated T antigen causing polyagglutination and red cell hemolysis. Activated T antigen is present in approximately 11–27% of neonates with NEC, with a greater frequency in more severe NEC (category III NEC 30% vs. II 4%) [331, 332]. The magnitude of the risk of T antigen in neonates with NEC is unclear, although many clinicians avoid transfusing plasma-rich blood products to these neonates and many blood banks screen plasma for antibodies to T antigen and release only plasma with low or no titers of T antigen to neonates with NEC. Nonetheless, any child with NEC who develops hemolysis after a transfusion should be investigated to identify the cause, not overlooking the possibility that activated T antigen is the putative agent [333].

Surgical intervention is required in 10–20% of neonates with NEC, increasing to 50% in very low-birth-weight neonates. The indications for surgery include serial examinations that indicate worsening physiological parameters or failure of medical treatment. The precise indications for surgery remain controversial; ideally, surgery is indicated for the presence of gangrenous bowel, before it has perforated [310]. However, there are no reliable metrics to define such a clinical scenario. Absolute indications for surgery include evidence of perforation, clinical deterioration despite maximal medical therapy, an abdominal mass with persistent obstruction or sepsis, and the presence of an intestinal stricture. Relative indications include abdominal tenderness, distension or discoloration where the clinical diagnosis may be in doubt, the finding of portal venous gas on plain abdominal X-ray, a fixed intestinal loop, and thrombocytopenia.

Surgical Approach

The surgical objectives are to control sepsis, to excise necrotic bowel, and to preserve intestinal length [310, 322]. A laparotomy remains the mainstay approach for most neo-

nates with NEC. In the very low-birth-weight group (<1000 g) with evidence of perforation, peritoneal drainage has been proposed as either an interim or definitive alternative to laparotomy, although a systematic review suggested that this was associated with increased morbidity and should be used as an interim approach only [334]. The clinical instability of these neonates warrants consideration of surgery on the NICU to avoid iatrogenic deterioration. Surgical options at laparotomy include resection with enterostomy, resection with primary anastomosis, a proximal diverting jejunostomy for extensive disease, and "clip and drop" or the watch and wait with possible "second look" laparotomy [310, 322]. The extent of the disease, the stability of the neonate, and the surgeons' experience/preference will determine which of these options are undertaken. For a stable neonate with focal or multifocal disease, a resection with anastomosis is appropriate. For an unstable neonate in whom the viability of the distal bowel is uncertain, a stoma may be fashioned. In the presence of pan-intestinal disease (>75% of the small and large bowel involved), either a proximal diverting jejunostomy or the "clip and drop" approach requiring a repeat laparotomy in the next few days is performed. NEC is responsible for one-third of the cases of surgical short bowel syndrome in NICU. Although mortality has been substantial in these neonates, a multifaceted approach to resting and preserving bowel function, nutrition, infectious prophylaxis, and surgical consultation dramatically improved survival [267]. A general guide for the ability of the gut to support enteral feeds long term is the presence of 30 cm of bowel with the ileocecal valve or 50 cm without [310]. In extreme cases where the entire intestine is necrotic, withdrawal of care may be an important consideration.

The neonatal liver is fragile and often enlarged in these infants. Aggressive perioperative resuscitation can result in hepatic engorgement and may result in capsular rupture and life-threatening hemorrhage. Surgical handling can also have similar catastrophic consequences. The laparotomy incision may be performed more caudally or obliquely especially in extremely low-birth-weight infants, to lie below the liver edge. Strict avoidance of liver instrumentation can help decrease the risk of hemorrhage. In the face of uncontrolled bleeding, ice and pack compression of the abdominal cavity should be considered.

Laparoscopy may be used as a diagnostic tool in NEC if the neonate is stable, if there are signs of obstruction, and if the diagnosis is uncertain. Some have attempted gasless laparoscopic surgery to diagnose and manage NEC in neonates with limited success [335].

Anesthetic Considerations

Laparotomy for NEC in a premature neonate <1000 g provides a significant challenge for the anesthesiologist. The potential for rapid blood loss in a neonate with cardiorespiratory instability, DIC, and sepsis requires meticulous preparation. In the operating theater, anesthesia may be induced using an opioid such as fentanyl in incremental IV doses of 5–10 mcg/kg up to 12.5–25 mcg/kg and/or ketamine 2–4 mg/kg and rocuronium [336]. The clearance of fentanyl decreases with decreasing gestational age in neonates with normal intra-abdominal pressure [337]. Inhalational anesthetics are infrequently used in neonates with NEC as these surgeries are often performed in the NICU without access to anesthesia workstations and because these neonates are often hemodynamically unstable. A balanced salt solution (10–20 mL/kg) should be administered before induction of anesthesia to prevent hypotension as anesthesia is induced. More recently, remifentanil has been investigated in preterm neonates [338, 339]. The duration of action of remifentanil in premature neonates between 24 and 41 weeks' gestation is similar to that in full-term neonates, 5–10 min. This has been attributed to the similar activity of nonspecific tissues esterases throughout gestation [340]. Animal evidence also suggests that remifentanil may effectively attenuate ischemic-reperfusion injury in the intestines [341]. If true in humans, remifentanil may provide a salutary effect in neonates with potentially ischemic bowel. Before anesthesia is discontinued, a longer-acting opioid should be administered to provide postoperative analgesia.

Surgery may be performed in the operating room or in the NICU (see Anesthesia Outside the OR, Chap. 12). Indications for surgery in the NICU include minor procedures (insertion of a peritoneal drain); a very small, unstable neonate; and ventilation with HFOV. For anesthesia in the NICU, a TIVA technique is required. In such cases, incremental doses of IV fentanyl (10–20 mcg/kg) or a remifentanil infusion, together with ketamine and rocuronium, should provide hemodynamic stability and adequate surgical conditions. The extent of the procedure depends on the hemodynamic stability of the neonate, and close cooperation among the surgeon, neonatologist/intensivist, and anesthesiologist is required at all times.

Inotropic support (dopamine, dobutamine, epinephrine, or norepinephrine) is often required, in neonates with NEC. In order to accurately monitor the responses to this support, arterial pressure monitoring is highly recommended. The inotropic support should be tailored to the neonate's requirements and titrated to the desired endpoint [342]. In addition, venous access large enough to rapidly deliver blood products should be secured. Albumin 5%, blood, platelets, and clotting factors may be required before or during surgery. Warmed IV fluid boluses of 10–20 mL/kg should be given depending on the clinical condition of the child and measured losses, guided by the results of arterial blood gas estimation. Since these neonates are often of very low birth weight, their albumin levels are reduced. Balanced salt solutions may be used to replace small fluid shifts but are best

limited in volume administered to preclude exacerbating pre-existing hypoalbuminemia and dilutional coagulopathy. If large volumes of fluid are required (up to 50 mL/kg), it is prudent to switch from balanced salt solutions to albumin and blood products early to maintain the hematological and coagulation profile. At the same time, care must be taken to avoid over-transfusing the child, as this could open a ductus arteriosus or risk catastrophic bleeding from a distended liver. The neonate may remain critically ill after surgery requiring full intensive care support. Mild controlled hypothermia may be a therapeutic option in neonates with multiple organ dysfunction [343].

Conjoined Twins

Introduction

Conjoined twins present an extreme clinical, logistical, and ethical challenge for both the surgical and anesthesia teams. Successful management of these children requires a multidisciplinary team in a close working relationship. Antenatal diagnosis is usually possible to prepare and meticulously plan for surgery at an experienced center. There is often a need for surgery to be performed after the first few months of life. Occasionally however, emergency procedures or investigations that require anesthesia may be required in the neonatal period, or very rarely can present unexpectedly after birth.

Epidemiology

Conjoined twins occur in 1.47 per 100,000 live births. Stillbirth is common with these defects. Females outweigh males by a factor of about 3 to 1 and are more likely to survive birth. Approximately 35% of live births die within 24 h of birth, with 18% surviving beyond this. Conjoined twins occur sporadically. The pathogenesis of conjoined twins is most likely from abnormal splitting of the blastocyst after the 12th day of gestation.

Conjoined or symmetric twins (as opposed to parasitic twins) are classified by their site of attachment. A commonly used classification system with eight subtypes was described by Spencer as listed in Table 9.10 [344] and illustrated in Fig. 9.22. A worldwide incidence of each type has also been reported [345–347].

Table 9.10 Conjoined twin variants

Type of conjoined twin	Incidence of variant (%)	Anatomical description
Thoracopagus	42	Face to face, joined thorax to umbilicus, always involves the heart
Omphalopagus	5.5	Umbilicus, never involves the heart
Pygopagus	1	Sacrum and perineum
Ischiopagus	1.8	Joined at the lower abdomen and has duplicated fused pelvic bones with external genitalia and anus always involved
Craniopagus	5	Joined at the skull and share meninges, does not include the face and trunk
Parapagus	2.9	Extensive side-to-side fusion, lower abdomen and pelvis ± thorax; two subvariants as shown in Fig. 9.10: diprosopus refers to duplication of the face (partial or total) and dicephalus refers to duplicate heads
Rachipagus	Extremely rare, 1	Dorsally fused and may involve cervical vertebrae and occipital bone
Cephalopagus	5.5	Head to umbilicus—extensive anomaly usually unsurvivable. Overall, fusion is predominantly on the ventral side (87%), less commonly dorsal (13%)

Presentation

Conjoined twins can be identified on antenatal ultrasound as early as 8 weeks' gestation, although false positives are common before 12 weeks. When the diagnosis has been confirmed, further antenatal imaging can assist with delineating the anatomy, including fetal MRI, echocardiography, and ultrasound. Delivery is ideally undertaken close to term in or near to a center with expertise in managing and separating conjoined twin. Surgical planning can start during the antenatal period. After birth and assessment, conjoined twins are divided into three groups based on their survival and urgency of surgery (Table 9.11)

Emergency procedures that may be anticipated for conjoined twins include those carried out to defunction bowel or relieve gastrointestinal or urinary tract obstruction. Rarely emergency separation is considered when severe cardiac defects require it or when one twin is dying. Such surgery carries a high mortality of 40–80%.

Larger defects are usually internally more complex. If organ function allows, they are separated closer to 1 year of age when the infant has grown in relation to the size of the defect. Cardiac involvement is associated with a poor prognosis. Conjoined twins may also present for anesthesia in the neonatal period for vascular access, for investigations for surgical planning, or for separation of very minor defects.

Management

The management of conjoined twins is complex and challenging. Ethical, legal, and potentially psychological challenges are ever present for the team, patients, and families in addition to the anatomical and physiological issues. Not all conjoined twins are amenable to surgery; many are unsuitable for separation because of ethical considerations or unfavorable anatomy. Safe management of conjoined twins requires a multidisciplinary team approach involving surgery, anesthesia, radiology, intensive care, pediatric medi-

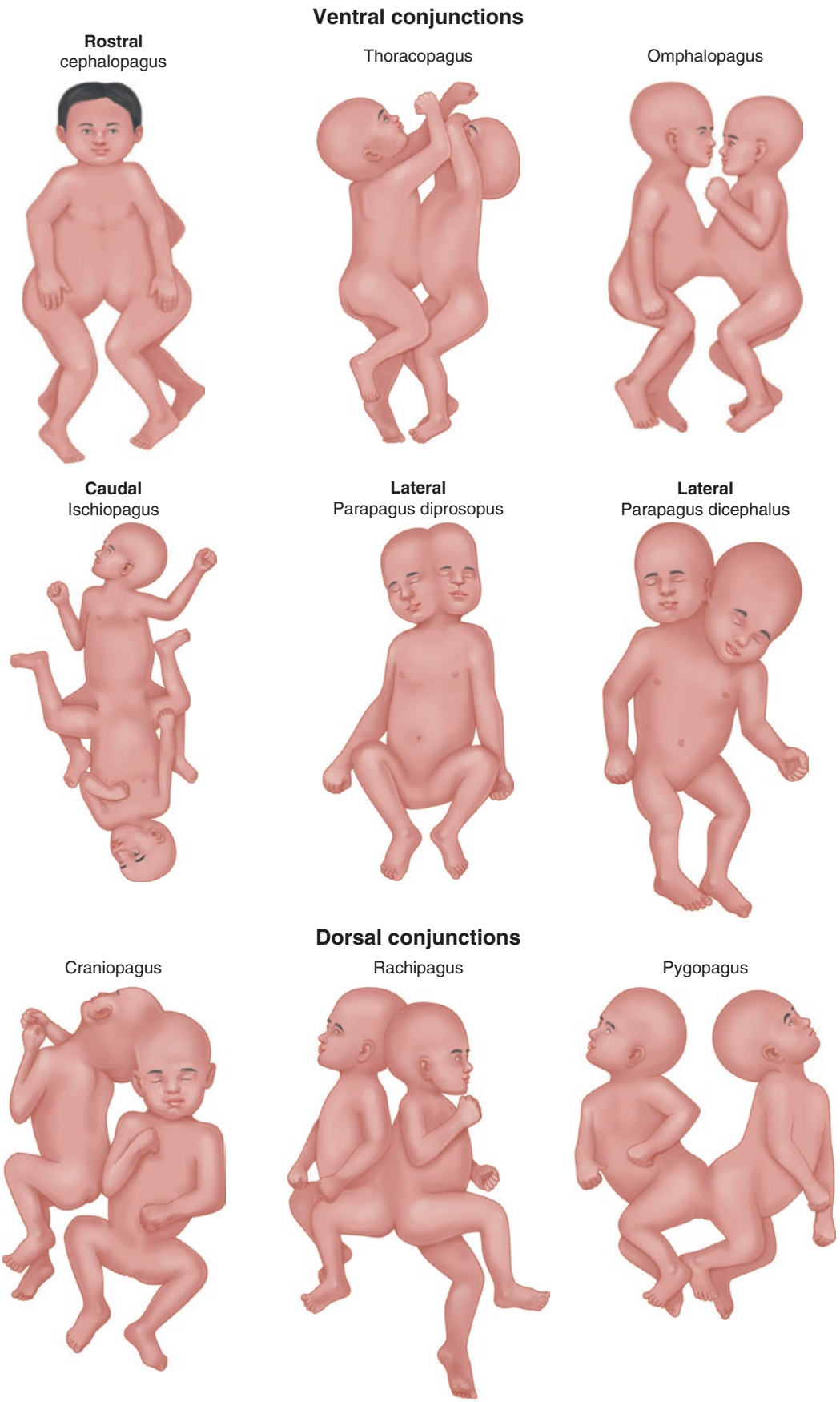

Fig 9.22 Pictorial illustrating each of the eight variants as described by Spencer, with two subvariants of parapagus [With permission. Pattanaik HP, Parida S, Mohapatra M Conjoined twin: review with a case report. Medico-legal update, October-December 2020, Vol 20, No.4]

Table 9.11 Results of treatment of conjoined twins

Group 1—unsurvivable or not for surgery
Group 2—planning for elective surgery
Group 3—requiring emergency surgery

cine, cardiology, ethics and legal team, nursing and other therapies, as well as the hospital communication or media team to support the family and to maintain confidentiality. Ideally there should be a designated team leader and the team should begin meeting as soon as a set of twins are identified in the event that urgent surgery is required during the neonatal period [348, 349].

The anatomical challenges relate primarily to the area of fusion and shared organs. Delineating the extent of organ involvement often requires detailed radiological investigations, some of which may require general anesthesia. These can include radionuclide tests, MRI, CT, angiography, ultrasound, and echocardiography [350]. Relatively new technologies such as 3D imaging and printing can assist surgical planning. Despite detailed preparation, unexpected issues are commonly encountered intraoperatively and the team need to be prepared for this.

Anesthesia Issues

Anesthesia may be required in the neonatal period for elective procedures, for emergency surgery, or rarely for full separation [351].

Logistics

Two distinct anesthesia teams will be required for each and every anesthetic until after separation. Two anesthesia machines and two sets of equipment will be required at every location. Some remote areas such as imaging suites will not be well set up for this and alternative arrangements need to be considered beforehand. Labeling or color coding machines and equipment are very helpful. Having personnel with conjoined twin expertise is vital, but sharing knowledge for succession planning is also very important since these cases are rare even in larger centers.

Airway

The orientation of conjoined twins can result in challenging airway management, particularly when face to face or where there is high thoracic involvement or neck abnormalities. Supraglottic airway devices can be useful for rescue management or for anesthesia for imaging. Information about airway management for separation surgery can be gathered during anesthesia for pre-separation investigations. If necessary, videolaryngoscopy, ENT assistance, or elective tracheostomy can be considered.

Vascular Access and Blood Loss

Separation surgery is long and can be associated with large fluid shifts and blood loss. In addition, veins can be challenging and can be lost during successive cannulations for investigations. Thoraco-omphalopagus twins will not have umbilical vessels that can be used for emergency neonatal access. Central access is optimal for major surgery, both intraoperatively and in the postoperative period. This should be jugular for thoracic and abdominal surgery. If necessary, interventional radiology can place longer term lines for nutrition, antibiotics, and sampling postoperatively, but these usually have narrow lumens and may be unsuitable for theater.

Preoperatively Assessment

Each twin should have a dedicated consultant anesthetist who will attend planning MDTs and undertake a detailed preoperative assessment of "their" twin. Counseling and consenting the parents need only be done once.

Useful preoperative investigations include complete blood count, coagulation profile, U&E and liver function tests (and other assessments of renal and hepatic function), fasting blood sugar, crossmatch, chest X-ray, and echocardiogram.

Theater Setup

As part of the preoperative planning, the anesthesia team should understand the surgical steps, which personnel will be involved and at what stage, and what positioning will be required. Care should be given to the setup of the equipment in the operating theater including the position of the anesthesia machines and ventilator tubing and lines. The surgical team need good access to the babies and the anesthesia team need to have secured the airways and any IV lines and be able to easily access these wherever possible. Theater lights and equipment such as diathermy, suction, or cell salvage will need to be considered for both twins.

Simulation with the full team can be extremely useful with a "dry run" including the use of mannequins for all steps from ward transfer through induction, operative procedures, and positioning to transfer postoperatively, being very helpful for planning and familiarity with the setup prior to surgery. This can also allow potential trouble points to be identified. Two full teams of staff (anesthetic, anesthetic assistants, surgeons, scrub staff, runners) are required for each twin and must be allocated. The use of different colored theater caps or similar can help identify each team's members [352].

For separation surgery one twin will require transfer to a separate operating table after separation for the reconstruction and will therefore usually be transferred to an adjacent theater. It is important to set this area up in advance and to decide which twin will move and how sterility will be maintained on transfer. The twin with the more robust cardiovascular circulation and physiology is often the designated twin to be moved which should be planned in advance.

Holding a thorough team brief on the day is vital so that the whole team can introduce themselves, establish roles, outline the plan for surgery, and discuss what may go wrong.

In the event of emergent surgery it may not be possible to follow all these steps but it is helpful for the whole department to know that a set of conjoined twins are in the hospital and to know who to call if there is an emergency. A verbal "dry run" in an emergency planning meeting is usually still possible even in truly emergent situations.

Conduct of Anesthesia

Conjoined twins share a circulation and shunting from one twin to another occurs. Sometimes this is very apparent preoperatively and sometimes this becomes apparent during anesthesia and surgery. It is rarely predictable from preoperative imaging, except where one twin has a cardiac defect. The degree of shunting can affect the rate of onset of anesthesia and the response to medications. Differing heart rates are common.

Despite this shared circulation, it is safest to consider each twin as an individual and the anesthetic management should proceed with that in mind.

Induction

Induction usually occurs in the operating theater unless the babies have already required intubation and sedation on the NICU. It can be helpful to ask other personnel to leave during anesthesia to avoid distractions since good communication is absolutely vital.

Despite the shared circulation, induction should occur simultaneously. Drug doses are calculated as half of the combined weight but each baby may show a different response. Either inhalational or IV induction is suitable but nitrous oxide should be avoided as it may distend the bowel. After securing venous access, neuromuscular blockade should be administered simultaneously.

Airway

Intubation should occur one after another. If there is difficulty maintaining an airway with a bag and mask, adjuncts should be used or an LMA can be inserted. Once the first of the twins is stabilized, the second twin should be positioned for tracheal intubation. On occasion, this will involve considerable manipulation of the first twin. Short handle laryngoscopes and videolaryngoscopy can be helpful. Prone positioning is likely at some stage so a reinforced or nasal tracheal tube is preferred; the nasal route is often preferred for long-term ventilation postoperatively. Both tubes should be well secured and auscultated in a range of positions.

Lines

As mentioned previously, large bore venous access is necessary for fluid and blood administration and for monitoring. Inotropes are commonly required in the presence of intracardiac shunting and cardiac management. Vasodilators may be required for hypertension after separation. Lines should be secured and every lumen should be accessible and all clips opened. Peripheral access is preferable in the upper limb since lower body blood vessels may be damaged or ligated intraoperatively.

Monitoring

Usual anesthetic monitoring should be applied before induction of anesthesia. An arterial line is inserted in both twins after tracheal intubation. This enables close hemodynamic monitoring and regular blood sampling to check fluid and acid-base status. Electrocardiographic monitoring may be difficult because of surgical access. Urine output can be difficult to monitor in the presence of pelvic abnormalities, during renal tract surgery, and because of the small size of the babies, but it should be recorded where possible or documented as being present. Temperature should be monitored and NIRS may be useful depending on the site of conjoining.

Fluids and Blood

Emergency neonatal abdominal surgery has been described elsewhere in the chapter. Fluid loss can be considerable. Fluid will need to be warmed and electrolytes and acid-base measured to assess adequacy of fluid replacement. Hourly maintenance fluid will also be required. Hypoglycemia is common in neonates and a dextrose-containing fluid should be infused throughout.

Surgery to separate the neonates is often quite prolonged, often exposing large sections of bowel and abdominal viscera for extended periods. Blood loss is common. Blood should be crossmatched for each twin and administered separately to each twin as a gold standard, despite part or all of their circulations are shared. This can be bypassed in an emergency and the same unit of blood safely administered to either baby before separation. As a result of shunting, one neonate may show an exaggerated response to blood or fluid administered compared with the other or have a diuresis.

Massive transfusion can be an issue. The neonatal myocardium is sensitive to hypocalcemia and this should be immediately treated and coagulopathies corrected.

Antibiotics

These should be administered according to surgical request and local policy and are continued into the postoperative period. Usually more than one dose will be required during long separation surgery.

Inotropes and Resuscitation

Surgical separation causes profound changes in shunting affecting preload and afterload. Inotropes are often required and these can include adrenaline and milrinone. Knowledge of any coexisting cardiac defect may influence inotrope selection.

In the unfortunate event of a malignant arrhythmia, cardioversion of one twin may result in an arrhythmia in the other; therefore, two defibrillators should always be available.

Surgical Considerations

The surgical principles should follow a similar approach to those for anesthesia with both twins considered separately. The anatomical arrangement will determine practicalities of surgery. Twins with cardiac involvement, which would not allow separation or with a single portal system, are not considered separable.

The specific surgical team will be determined by the organs involved and for those with abdominal and pelvic fusion will involve the general surgeons, the urologists, plastic surgical team, and potentially orthopedic surgeons. The exact surgical procedures which may be required can be partially planned from the imaging although it can be difficult to ascertain the exact level of bowel involvement and fusion until surgery. The initial incision for separation will usually be from the "back" through skin and muscle, requiring the patients to then be turned over while maintaining sterility (with careful preservation of vascular access and the airways) to allow further incision, exploration, and proceeding with the separation. This helps prevent deviation from the midline which can be difficult due to the variable and complex anatomy.

Once separation has been performed, then one of the twins is transferred to a separate operating table and then usually taken to an adjacent theater. The decision on which twin is moved is often based on the anticipated stability of the twins but may also be influenced by practical considerations such as positioning of doorways and corridors to allow the smoothest transition. All repositioning and transfer points are critical moments requiring meticulous attention. Where possible shared vessels and circulation points are identified and then gently temporarily clamped to assess the physiological response. This allows the anesthesiologist time to prepare the appropriate support and response before permanent ligation.

After separation, the main surgical consideration is reconstruction. There may be significant body wall defects requiring the use of prosthetic patches, muscle flaps, and other advanced reconstructive procedures. Complete body cavity closure may not be possible at the initial separation surgery and further procedures may be serially required over the following days or weeks.

Separation surgery can be an extremely lengthy procedure and appropriate breaks and relief for the team members when required should be considered where possible.

As for anesthesia, there should be two separate operative reports that must contain clear descriptions of each twin's newly reconstructed anatomy after separation to allow appropriate individual ongoing management.

Postoperative Care

Postoperatively the neonates will be best managed in an ICU setting, even after relatively simple bowel defunctioning surgery. After separation surgery, the trachea remains intubated, and the lungs ventilated. On occasion, the neonate may remain paralyzed to allow recovery and ongoing fluid management. Large wounds are usually closed with synthetic polyethylene or polypropylene material and require serial "tucks" to achieve full skin closure.

Summary

Neonatal anesthesia for conjoined twins is very rare and usually carried out at a specialist center for investigations and emergency surgery. Excellent communication, planning, and multidisciplinary teamwork are essential as logistical challenges exist at every stage. Airway management, vascular access, and blood loss are major considerations even for the most experienced anesthesiology team.

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Neurosurgery and Ophthalmology

10

David N. Levin and Sulpicio G. Soriano

Introduction

The central nervous system (CNS) and visual system undergo extensive structural and physiological changes during the first year of life. Neonates have unique features in cranial bone development, cerebrovascular physiology, and congenital lesions, which impact the conduct of anesthesia. Neonates are at greater risk than any other age group for morbidity and mortality during the perioperative period due to respiratory and cardiac-related events [1]. This risk is increased further when the indication for surgery includes neuropathology [2]. Therefore, an organ system-based evaluation, detailed in preceding chapters, must be performed to rule out congenital anomalies or coexisting pathology that may impact the conduct of anesthesia and outcome.

Development of the Central Nervous and Visual System

Embryology

The development of the central nervous and visual system occurs in parallel early in gestation [3]. Derangement in this process leads to congenital lesions of the CNS and eye [4]. Therefore, a basic understanding of embryology will provide insight into a majority of neurosurgical and ophthalmological lesions.

Neurulation is the fundamental process where the neural plate folds and bends dorsally to form the neural tube [5]. Primary neurulation occurs when the neural plate forms the ectoderm folds and fuses dorsally. The walls of neural tube give rise to the brain and spinal cord. The neural canal develops into the ventricles and central canal of the brain and spinal cord. Fusion of the cranial neural folds and closure of the cranial neuropore give rise to the forebrain, midbrain, and hindbrain. Closure starts near the cervical spine region and extends cephalad and caudad. Closure of the neural tube begins at 22–23 days of gestational age, with complete closure around days 26–27. Failure of the anterior neuropore to close results in anencephaly and dermoid/dermal sinus tracts, whereas posterior defects lead to encephaloceles and myelomeningoceles. Most defects occur along the lumbosacral region but can arise at any level, including the thoracic and cervical segments. Secondary neurulation starts after primary neurulation is completed and forms the lower sacral and coccygeal segments. Derangements in this progression can lead to closed spinal dysraphism (spinal bifida occulta and tethered cord). The incidence of neural tube defects is approximately 2–5/1000 live births. Outcome studies reveal increased perioperative morbidity, mortality, and cognitive deficits in neonates with congenital neurological lesions [2, 6–8].

Eyes develop between the 3rd and 10th week of gestation. The retina, iris and ciliary body epithelia, optic nerve, smooth muscles of the iris, and a portion of the vitreous humor arise from the cephalic region of the neural tube ectoderm. Surface ectoderm gives rise to the lens, conjunctival and corneal epithelia, eyelids, and the lacrimal apparatus. The remaining ocular structures arise from the mesenchyme.

Cerebrovascular Physiology

Cerebral autoregulation is fully developed in the healthy term neonate. However, in the neonate with coexisting disease such as prematurity, hypoxic brain injuries, intracranial hemorrhage, traumatic brain injury, neurovascular anomalies, inflammatory processes, and congenital heart, cerebral

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hemodynamics may be seriously impaired. Although the theoretical autoregulatory range of blood pressure in infants is lower than that in adults due to the relatively low cerebral metabolic requirements and blood pressure in infancy, recent evidence demonstrated heterogeneity in the lower limit of autoregulation in pediatric patients [9]. Furthermore, cerebral autoregulation may be absent and replaced by pressure-passive CBF in critically ill, premature, low gestational age, and/or low birth weight neonates [10]. Systolic arterial blood pressure is a poor indicator of cerebral perfusion pressure in these patients, and the diastolic closing pressure may be a better surrogate [11]. Extremes in blood pressure can lead to cerebral ischemia and/or intraventricular hemorrhage and dictate rigorous control of hemodynamics.

Cerebral blood flow (CBF) in the healthy neonate is significantly less than that in adults and doubles in the first 2 days of life in parallel with increases in cardiac output [12]. Cerebral metabolic requirement for oxygen ($CRMO_2$) increases with gestational age [13]. However, non-invasive indices of $CRMO_2$ demonstrate that neonates with birth injuries have significantly greater cerebral requirement for glucose (CMRGlu), which continues to increase with gestational age. These ontological changes in $CRMO_2$ and CMRGlu are reflected in CBF values derived from brain perfusion CT scans [14]. The variance in these values is as great as those in the CBF and the lower limit of autoregulation noted above. Thus, population-based averages are poor surrogates for individual target values and requirements. Cerebrovascular reactivity to carbon dioxide appears to be normal in healthy neonates, but may be deranged in the setting of perinatal asphyxia or prematurity [15]. Inspired concentrations of oxygen (FIO_2) have an impact on CBF [16]. Premature neonates are also vulnerable to the detrimental effects of high FiO_2 due to liberation of reactive oxygen species leading to bronchopulmonary dysplasia and retinopathy of prematurity [17].

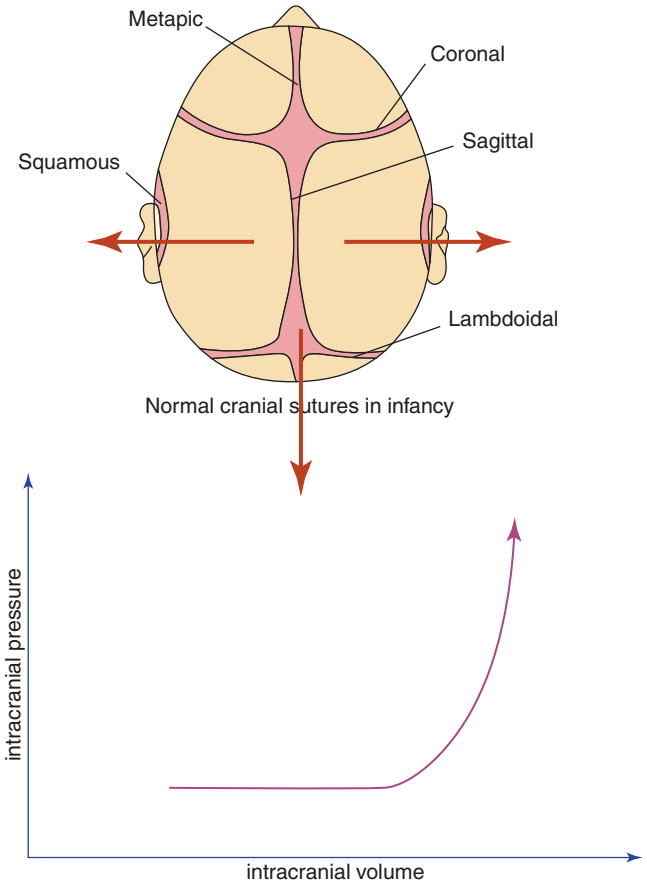

Fig. 10.1 Compliant and open sutures and fontanelles permit slow expansion on the intracranial volume and gradual increases in intracranial pressure. Intracranial hemorrhages or obstructed cerebrospinal fluid flow led to life-threatening elevations of intracranial volume and pressure

Anatomy of the CNS and Eye

Cranium

The intracranial space in neonates is compliant. The compliance stems from the presence of open fontanelles and fibrous unfused sutures. The posterior and anterior fontanelles close in sequence, the former from 0 to 4 months and the latter from 12 months to 18 months, respectively. Therefore, gradual increases in intracranial mass due to hydrocephalus, hemorrhage, and tumor may not cause symptomatic increases in ICP due to compensatory distension of the fontanelles and widening of the cranial sutures (Fig. 10.1). However, given the diminutive neonate and infant intracranial volume, acute increases in cranial content due to blood or cerebrospinal fluid can still result in life-threatening intracranial hypertension [18, 19]. Conversely, premature ossification of the sutures leads to a variety of craniosynostoses, which are best surgically corrected early in infancy with endoscopic techniques or cranial vault remodeling at a later age [20, 21].

Neonates are also distinguished in that their calvarium remains open after birth. This allows parenchyma and ventricles to grow without increasing pressure within the skull. Fontanels oscillate with the heart rate, which reflects intracranial volume expansion with each cardiac cycle. The arachnoid villi begin to develop after birth, playing an important role in resorbing CSF in adults [2]. Premature neonates and those with underlying calvarial or parenchymal pathology exhibit abnormal dural compliance and may be more susceptible to increased ICP [3]. Between 50% and 80% of the cerebrospinal fluid (CSF) surrounding the brain and spinal cord is secreted by the choroid plexus, which lines the floor of the lateral ventricles and the roof of the third and fourth ventricles. Up to 30% of the CSF can be formed in other sites such as ependyma, brain parenchyma, and endothelium of cerebral capillaries. The CSF produced by the choroid plexus flows from the lateral ventricles, through the

interventricular foramen of Munro into the third ventricle and then into the cerebral aqueduct of Sylvius to the fourth ventricle. It emerges from the interior of the brain through the two lateral foramina of Luschka and the single medial foramen of Magendie to enter the subarachnoid space. The CSF is absorbed by the arachnoid villi. The mean production rate of CSF in children is about 0.35 mL/min. CBF and CBV are much more important determinants of ICP than is the volume of the CSF.

Spine

The spinal cord and CSF are contained within the cylindrical vertebral canal. The spinal cord is the caudal continuation of the brainstem. Its caudal tip reaches the intervertebral space of L3 at birth and then slowly migrates to the adult level of L1–L2 by 8 years of age, though there is a wide inter-individual variability [1]. Incomplete development of the spinal canal (spinal dysraphisms) leads to tethered cord syndromes.

Eye

The neonatal visual system is comprised of the sclera, uvea, and retina. These structures develop between the third and tenth week of gestation. During the sixth or seventh weeks of gestation, the mesenchyme evolves into an inner, vascular layer that forms the choroid and an outer fibrous layer known as the sclera. The sclera is the outer layer of the eye, with the transparent anterior portion delineating the cornea. The uvea is the vascular middle layer that contains the iris, ciliary body, and choroid. It has multiple functions that include immunity, nutrition, oxygen and carbon dioxide exchange, light transmission, production of aqueous humor, and visual accommodation, most of which are controlled by the autonomic nervous system. The neural tube ectoderm differentiates into the retina, with the posterior outer layer producing the pigmented layer and the posterior inner layer producing the neural layer of the retina.

Neurosurgery

Congenital Anomalies

Congenital CNS anomalies typically occur as midline defects. These neural tube defects may arise anywhere along the neural axis from the head (cranial dysraphism) to the spine (spinal dysraphism). It may be relatively minor and affect only superficial bony and membranous structures, or it may include a large segment of malformed neural tissue. These lesions are associated with type II Chiari (Arnold-Chiari) malformations, hydrocephalus, and neurologic deficits. Cervical cord and brainstem compression are possible in infants with concomitant type II Chiari malformations. After birth, the cervical and spinal defects are usually covered with sterile, saline-soaked gauze in order to keep the lesion moist and clear and the neonate is positioned prone to avoid direct pressure on the defect.

Cranial Dysraphism

Cranial dysraphisms or encephaloceles are characterized by a sac-like calvarial defect that arises anywhere from the nose to the occiput. The former can manifest as nasal polyps that protrude through the cribriform plate. Cranial meningoceles contain cerebrospinal fluid and meninges. The presence of neural elements in the meningocele classifies this cystic lesion as meningoencephalocele. Encephaloceles are classified by their location on the cranium, with sincipital lesions in the frontal calvarium and occipital encephaloceles sited posteriorly. Primary encephaloceles are often diagnosed in utero by fetal ultrasonography, with large encephaloceles delivered by elective cesarean section. Most small encephaloceles have minimal neurological deficits, whereas those with large lesions may present with cranial nerve abnormalities and subsequent developmental and growth delay, poor feeding, blindness, and seizures.

Preoperative diagnostic imaging is essential to delineate the content and margins of the lesion. Sedation or general anesthesia is required for computed tomography (CT) and magnetic resonance imaging (MRI) scans. Encephaloceles can be associated with hydrocephalus and other craniofacial and brain abnormalities such as anencephaly, microcephaly, ataxia, Meckel's, and amniotic band syndrome.

Encephaloceles will continue to enlarge after birth. Surgery can be delayed and performed in stages, if the overlying skin is intact. Innovations in neonatal care and surgical techniques, including image guidance and multidisciplinary reconstruction techniques, have improved the outcome for patients.

Sincipital encephaloceles usually contain fibrous tissue, which can be safely transected at the level of the skull and the defect closed primarily. Nasal or sphenoethmoidal encephaloceles are rare. They are characterized by a skull base defect around the sella turcica. Large lesions may obstruct the airway and compromise pituitary function, whereas smaller lesions may be undetected throughout infancy. Other defects including midline nasal masses including nasal polyps, dermoid sinus cyst, and tumors should be included in the differential diagnosis. Image guidance based on 3-dimensional image reconstructions and radionuclide ventriculography is useful. The resection and closure can be difficult during transpalatal surgical approaches due to exposure and inadequate soft tissue for closure. Other surgical procedures include transcranial, subfrontal, and endoscopic transnasal approaches. The postoperative course may be complicated by CSF leaks, meningitis, visual impairments, and endocrine derangements.

Occipital encephaloceles may contain functional brain tissue that needs to be preserved. Most encephaloceles with

substantial neural tissue herniating through large cranial defect require an expansion cranioplasty and a plastic surgeon to create split thickness calvarial grafts. When primary closure is not possible, a staged secondary repair is an option. Large occipital encephaloceles may be associated with twisting of the brainstem, lobar herniation, and hydrocephalus.

Spinal Dysraphisms

Spinal dysraphisms are lesions in which the dorsal midline structures fail to fuse during embryogenesis. Spina bifida aperta is easily identifiable by the sac-like lesion containing meninges (meningocele) or neural tissue and meninges (myelomeningocele). Spina bifida occulta has an intact skin surface but a small gap in the bony spine, with spinal cord and nerve root usually uninvolved. These spinal defects can occur anywhere along the vertebral column, although lumbar and low thoracic defects are most common. Rachischisis is the most severe form of dysraphism where the posterior neuropore fails to fuse. A protruding membranous sac containing meninges, CSF, nerve roots, and a dysplastic spinal cord often protrudes through the defect in meningocele or myelomeningocele. These congenital lesions are surgically closed during the neonatal period. However, residual lesions and scar tissue can manifest as tethered cord syndrome (TCS) due to traction on the spinal cord. This may lead to permanent neurological deficit distal to the lesion, and requires surgical untethering when symptoms persist.

Prenatal ultrasonography affords early diagnosis and planning for elective cesarean delivery and expeditious closure of meningomyeloceles. These lesions may also be repaired in utero at specialized fetal surgery centers [22]. In order to minimize the risk of infection, meningomyeloceles undergo primary closure of the defect within the first 24 h of life. These lesions are often associated with a type II Chiari malformation where both the cerebellum and brain stem tissue protrude into the foramen magnum.

Since type II Chiari (Arnold-Chiari) malformations predispose patients to hydrocephalus, insertion of a ventriculoperitoneal shunt may be combined with the initial surgery. Alternatively, a ventriculoperitoneal shunt may be inserted a few days later – or deferred if there is no evidence of hydrocephalus. Patients with thoracic lesions may have poor autonomic control below the level of the defect.

Anesthetic Management

Preanesthetic Evaluation

Cranial and spinal dysraphisms are heterogeneous lesions and mandate an individualized approach based on the severity and location of the defect. Therefore, a thorough review of the antenatal history, birth history, prematurity, comorbidities, and other congenital anomalies should be completed prior to surgery (Chap. 2). Some neonates with encephaloceles may have tenuous respiratory function due to direct airway obstruction or impairment of the pontomedullary respiratory control center. Depending on the size of the lesion and extent of the surgical procedure, significant blood loss should be anticipated during both the intra- and postoperative period.

Intraoperative Management

Positioning the neonate for induction of anesthesia can be challenging. Anesthesia can be induced with a propofol, but hypotension with resultant cerebral ischemia might ensue due to the lack of surgical stimulation [23]. Reducing the dose of propofol and adjuvant opioids for induction and adding a concurrent intravenous fluid bolus can mitigate the hypotension. In most cases, tracheal intubation can be performed with the neonate in the supine position with the defect supported with foam or gel head rings so there is no direct pressure on the lesion. Manipulation of these lesions should be limited because of the risk of rupturing the thin membranes. For very large defects, it may be necessary to place the infant in the lateral decubitus position for induction and tracheal intubation. The left lateral position is the preferred position so the tongue can fall to the left away from the side of the mouth where the laryngoscope blade is inserted. The Miller blade is inserted into the mouth via the right commissure for direct laryngoscopy. Intubation may be more difficult in the lateral position (only use the left lateral decubitus) in some neonates, requiring the use of a flexible fiberoptic bronchoscope or video laryngoscope.

Encephaloceles are associated with compromised airways to varying degrees. Effective mask ventilation may be impaired by protruding lesions of sincipital encephalocele and may hinder effective mask ventilation. In these patients, difficult airway precautions and techniques should be applied during induction of anesthesia [24]. Gigantic encephaloceles may prohibit proper positioning of the neonate for tracheal intubation. Some fluid-filled encephaloceles can be decompressed by aspirating cerebrospinal fluid with a sterile needle and syringe under ultrasound guidance. Alternatively, giant occipital encephaloceles can be suspended through a pediatric horseshoe headrest. Mask ventilation may be difficult in this position, so an assistant can support the head as the anesthesiologist applies a mask seal.

Surgical repair is performed in the prone position so the patient's face should be well supported by padded foam on a horseshoe headrest to prevent direct pressure on the eyes and mouth. Since the airway will be inaccessible during repair of occipital encephaloceles, nasotracheal intubation may be more secure and minimizes the risk of dislodging the tube. Prone positioning for the surgery requires careful

padding to prevent increased abdominal pressure and to protect eyes and other pressure points. We recommend nasotracheal intubation, fixing the tube with tape that would remain sealed in the presence of any liquid prep solutions and Mastisol or a similar adhesive. It is paramount to support the breathing circuit with tape to the horseshoe when the neonate is positioned prone as any downward pull may dislodge the tube from the trachea.

Ensuring adequate oxygenation delivery to the developing brain is the cornerstone of neonatal neuroanesthesia and critical care [25, 26]. Typically, blood loss during surgery is not significant enough to necessitate blood transfusions. However, the risk of bleeding and venous air embolization is greater in those with larger cranial defects. Therefore, multiple intravenous lines and an arterial catheter should be inserted when a large blood loss is anticipated. Occasionally, rotational or myocutaneous flaps may be required for closure of large defects. Respiratory parameters and oxygenation should be carefully monitored during primary closure of large defects because tight skin closure may compromise tidal volume and reduce venous return. Significant hypotension is typically due to blood and cerebrospinal fluid losses, but also can be a manifestation of hypothroidism, adrenocortical deficiency, or diabetes insipidus. Neonates who develop diabetes insipidus should be treated with a vasopressin infusion and urinary output replaced with crystalloid. A Foley catheter and an arterial line should be considered for any complex lesions or prolonged surgery. If the risk of a postoperative CSF leak is substantive, a ventricular drain may be inserted. With any flap-based closure on a vascular pedestal, meticulous fluid management aimed at maintaining perfusion while limiting edema needs to be employed. Similarly, vasopressors may be implicated in failed graft viability and should be discussed with the surgical team if and when their use is contemplated.

Postoperative Management

Since most of these patients are neonates, postoperative observation should be in a neonatal intensive care unit (NICU) setting. The decision to extubate the trachea is dictated by the degree of blood loss, fluid and blood administration, and neurological status of the neonate. Patients with large sincipital encephaloceles should go to an intensive care unit postoperatively to be closely monitored for adrenal cortical deficiency, diabetes insipidus, and airway obstruction. Mild sedation may be required for some pediatric patients should tracheal intubation and mechanical ventilation be continued.

Persistent CSF leaks may occur in repaired encephaloceles and may be confused with normal sinus drainage. Some patients may need additional surgery or have a ventriculostomy drain placed. In some complex occipital encephalocele and large myelomeningocele repairs, it is preferable to recover the patient in the prone position to avoid pressure on the incision. The patient will often continue to lose blood into the surgical site and require ongoing monitoring and treatment for anemia during the postoperative period.

Hydrocephalus

Hydrocephalus is the most common affliction of pediatric neurosurgical patients [27]. It has been defined as "an active distension of the ventricular system of the brain related to inadequate passage of CSF from its point of production within the ventricular system to its point of absorption into the systemic circulation." [28] Hydrocephalus is primarily due to an accumulation of CSF within the ventricular system of the CNS by congenital lesions, tumors, or secondary injury. Multiple etiologies and classifications exist—all of which promote the concept that all ventriculomegaly is "obstructive" in the sense that CSF absorption can be impaired by structural blockage or reduced physiological transport at the arachnoid membrane and its granulations, cranial nerve lymphatics, and capillaries of microvessels. Two subcategories for hydrocephalus are recognized: obstructive or communicating. Obstructive or noncommunicating hydrocephalus is an obstruction within the ventricular system or at the fourth ventricular outflow. Communicating hydrocephalus results from impaired circulation through the subarachnoid spaces (e.g., when the flow of CSF is blocked downstream of the ventricles) or diminished absorption into the venous system.

Pathological increases in CSF production or decreases in reabsorption can also lead to hydrocephalus. Congenital and neonatal hydrocephalus can be attributed to several developmental abnormalities or insults including neural tube defects, infection, intraventricular hemorrhage, trauma, and tumors. Hydrocephalus occurs when CSF cannot be absorbed at a rate sufficient to prevent its accumulation within the ventricular system, forcing the cerebral ventricles and occasionally the subarachnoid spaces to expand. In addition, hydrocephalus can occur as a result of the overproduction of CSF, as seen with choroid plexus papillomas.

Hydrocephalus is ideally managed by ameliorating the underlying problem. If this is not possible, however, surgical implantation of a drain or shunt may be necessary. The most common place to drain CSF through an implanted shunt is the peritoneal cavity, but the right atrium or pleural cavity has also been used. Although implantation of a ventriculoperitoneal shunt is relatively straightforward, perioperatively, patients may be at increased risk for aspiration of gastric contents caused by the combination of altered mental status and recent peritoneal manipulation. Venous air embolism (VAE) may occur during placement of the distal end of

a ventriculo-atrial shunt if the operative site is above the level of the heart.

Premature neonates can develop hydrocephalus secondary to intraventricular hemorrhages [29, 30]. The severity of post-hemorrhagic hydrocephalus is assessed by serial head ultrasounds. Accumulated CSF can be temporarily drained by placement of a ventricular reservoir or ventriculo-subgaleal shunt in very premature neonates [31, 32]. A ventriculo-subgaleal shunt diverts CSF through a small gauge tube from the ventricle into subcutaneous tissue. Diversion of CSF is the permanent treatment for hydrocephalus. However, placement of a ventriculoperitoneal shunt is limited by the size of the patient and increased risk of shunt failure. The distal end of the shunt will also migrate as the child grows. Hence, temporary shunts are used in the smallest of neonates with permanent diversion of CSF via a ventriculoperitoneal shunt reserved for older infants.

Infants with hydrocephalus can be treated with endoscopic ventriculostomy on the floor of the third ventricle followed by cauterization of the choroid plexus to attenuate excessive production of cerebrospinal fluid [33–35]. Recent advances in endoscopic techniques are being used to perform endoscopic third ventriculostomy (ETV) with the option of cauterization of the choroid plexus to moderate cerebral spinal fluid production [33–35].

Anesthetic Management

The common symptoms of hydrocephalus include a rapid increase in head circumference, irritability, sleepiness, nausea, and vomiting, and downward deviation of the eyes (known as "setting sun phenomenon") due to paresis of upward gaze is observed in 40% of children with obstructive hydrocephalus. Acute obstruction of a ventricular shunt requires urgent treatment because an acute increase in intracranial pressure in the relatively small cranial vault of the infant and child can have devastating neurologic and cardiorespiratory consequences.

The anesthetic management of these patients depends on the acuity of the patient's symptoms. Intravenous access is typically in place in the NICU and induction of anesthesia and tracheal intubation is facilitated with propofol and a non-depolarizing muscle relaxant. Judicious dosing of propofol is essential because it can cause prolonged hypotension in an unstimulated neonate [23]. Venous air embolism may occur during placement of the distal end of a ventriculo-atrial shunt.

Technological advances in minimally invasive surgery entered the realm of pediatric neurosurgery. These techniques include endoscopy and stereotactic guided insertion of intracranial devices. Given the relatively small size of the cranial vault in pediatric patients, life-threatening intracranial hypertension can occur insidiously.

Neuroendoscopic techniques have been utilized for treatment of hydrocephalus and tumor biopsies [33, 34, 36]. Precise insertion of ventricular shunt catheters can be facilitated with endoscopy as well. Despite the relative safety of this procedure, hypertension, arrhythmias, and neurogenic pulmonary edema have been reported in conjunction with acute intracranial hypertension due to lack of egress of irrigation fluids and/or manipulation of the floor of the third ventricle.

Tumors

Brain tumors in neonates are rare and develop during the perinatal period [37]. Fewer than 2% of brain tumors occur in neonates and develop slowly during the antenatal period. Most of these tumors are infratentorial, comprised of cell types that differ from brain tumors in older children: [38] teratomas comprise about one-third of the tumors, with the remainder being choroid plexus tumors, embryonal tumors (including medulloblastoma), and astrocytomas [39]. These lesions are initially detected during antenatal ultrasounds and subsequent fetal magnetic resonance imaging (MRI) for greater detail. Clinical presentation of these lesions includes macrocephaly, bulging fontanelles, hydrocephalus, cranial nerve palsies, seizures, and lethargy. These neonates should be admitted to the NICU for cardiorespiratory monitoring. Imaging modalities should be utilized early once the neonate is stabilized. Initially cranial ultrasound and CT of the head are indicated with MRI to delineate the tumor and the adjacent structures and rule out vascular malformations and parenchymal hemorrhages [40]. Most neonates will tolerate CT and MRI procedures with swaddling after a "feed and sleep" approach. However, sedation or general anesthesia may be required for more extensive protocols. The risk of surgery and anesthesia is great in the neonate. Therefore, rigorous surgical planning that includes managing hydrocephalus and possible congestive heart failure in large vascular tumors is indicated. Endoscopic techniques to biopsy the tumor to determine the tumor type and temporize the hydrocephalus should be considered to minimize morbidity. However, gross total resection of low-grade tumors is associated with more favorable survival rates [41].

Anesthetic Management

Hemodynamic stability during intracranial surgery requires careful maintenance of the patient's fluids and electrolytes and careful dosing of anesthetics to preserve adequate cerebral perfusion pressure. Since the lower limit of cerebral autoregulation in neonates is unknown, they are at risk for cerebral hypoperfusion especially when they are deeply

anesthetized during periods of massive blood loss. Given the risk for significant blood loss associated with many neurosurgical procedures, consideration should be given to site two large bore intravenous lines (22ga) and radial arterial access (Chap. 7). Central venous pressure access is rarely warranted in the superior vena cava distribution as any line in a major vessel may obstruct venous drainage, resulting in increased intracranial pressure. Femoral venous access may be used in its stead. A Foley catheter is particularly important if a diuretic is planned. Serial measurements of the hematocrit should be collected to assess for insidious blood loss. Typed and cross-matched blood should be available for all major craniotomies. A greater percentage (up to 25%) of cardiac output is directed toward the head. Therefore, normovolemia should be maintained throughout the procedure. Normal saline is commonly used as the maintenance fluid during neurosurgery because it is mildly hyperosmolar (308 mOsm/kg) and it theoretically attenuates brain edema. However, rapid infusion of a large amount of normal saline (30 mL/kg per hour) is associated with hyperchloremic metabolic acidosis [20]. Balanced crystalloids have been shown to prevent hyperchloremic acidosis when compared with normal saline [21]. Preoperative glucose-containing solutions may be included intraoperatively, especially in premature neonates since hepatic glucose stores may be inadequate to maintain euglycemia. Preferably, serial glucose concentrations should be monitored as hyperglycemia may exacerbate a neurologic injury should it occur during tumor resection. Acute hyperventilation and careful patient positioning to maximize cerebral venous drainage can minimize brain swelling [22]. Should these maneuvers fail however, mannitol can be given at a dose of 0.25–1 g/kg intravenously. This agent transiently alters cerebral hemodynamics and increases the serum osmolality by 10–20 mOsm/kg [23]. However, repeated dosing can lead to extreme hyperosmolality, and renal failure and exacerbate brain edema. Furosemide is a useful adjunct to mannitol for decreasing acute cerebral edema and has been shown in vitro to prevent rebound swelling caused by mannitol [24]. Hypertonic saline (3%) decreases ICP and maintains cerebral perfusion pressure in pediatric traumatic brain injury and recently was shown to more favorably affect cerebral hemodynamics than mannitol [42, 43]. However, all diuretics interfere with the ability to use urine output as a guide to intravascular volume status.

Massive blood loss should be aggressively treated with crystalloid and blood replacement as well as vasopressor therapy (e.g., dopamine, epinephrine, norepinephrine). In essence, massive blood loss during resections of tumors and vascular malformations (see below) predisposes the neonate to high-output congestive heart failure (CHF) during rapid infusion of blood products and crystalloid. Therefore, background infusion of an inotrope, dopamine or epinephrine, with vigilant titration is essential in maintaining cardiac output and systemic perfusion during this vulnerable period. The massive blood transfusion protocol of your institution should be activated in order to engage the blood bank. Transfusion of 10 mL/kg of packed red blood cells can be expected to increase hemoglobin concentration by 2 g/dL. Neonates are susceptible to dilutional thrombocytopenia and hypocalcemia in the setting of massive blood loss and blood product transfusions. The hypocalcemia is a result of the exogenous citrate used as anticoagulant in many blood products. Washing red cells can theoretically mitigate hypocalcemia, although the citrate content of plasma exceeds that in packed red blood cells. Administration of 5–10 mL/kg of platelets can be expected to increase platelet count by 50,000–100,000 cells/mm^3. Fresh frozen plasma and cryoprecipitate should also be administered to replenish clotting factors. The routine use of the antifibrinolytic agent, tranexamic acid, has been shown to decrease blood loss [44].

Vascular Anomalies

Intracranial vascular anomalies are rare in neonates but may be late clinical manifestation of insidious perinatal lesions. The most severe lesions are high-flow arteriovenous shunts that predispose afflicted neonates to high-output CHF [45]. These lesions are initially managed with endovascular techniques (EVT), which entail catheter-based angiography and embolization of neurovascular lesions [46]. Indications for therapeutic neuro-interventional procedures include embolization of intracranial vascular anomalies, such as arteriovenous malformations (AVM) or arteriovenous fistulae and aneurysms, targeted injection of intra-arterial chemotherapy for tumors, and pre-surgical embolization of both AVMs and tumors of the head and neck. Observation and medical management of mild CHF can delay these treatments until the patient is 5–6 months of age. However, urgent perinatal interventions are indicated if the neonate has refractory CHF, pulmonary hypertension, or pulmonary edema.

Perinatal Stroke

The causes of perinatal strokes in decreasing order of incidence include arterial ischemic infarction, cerebral sinovenous thrombosis, and intraventricular hemorrhage [47]. The initial management of presenting symptoms—seizures, hemodynamic instability, and respiratory compromise—is paramount. Sedation or general anesthesia may be required for MRI studies in order to delineate the extent of the lesion. These neonates are primarily monitored and managed expectantly for symptoms of seizures, hydrocephalus, and intracranial hemorrhage.

Vein of Galen Malformation

Vein of Galen malformations (VOGM) are congenital arteriovenous malformations between choroidal arteries and the precursor of the vein of Galen [48]. Patients with VOGM may present with high-output CHF, pulmonary hypertension, and/or hydrocephalus. Given the complex and unstable nature of this lesion, a multidisciplinary team composed of neonatologists, neuro-interventionalist, neurosurgeons, and anesthesiologists should work together to develop a comprehensive management strategy [49].

Preoperative Management

Since the most severe presentations of VOGM are accompanied with high-output CHF and respiratory failure, preprocedural optimization of these conditions should be managed in the neonatal or pediatric intensive care unit (NICU/PICU). Titration of inotropic support with dopamine or epinephrine and intravenous fluids should be guided by invasive blood pressure monitoring via an arterial catheter. The neonate may require tracheal intubation and mechanical ventilation as the CHF worsens.

Intraoperative Management

General anesthesia is mandatory for neuro-interventional procedures in these vulnerable neonates. Hemodynamic and respiratory support established in the NICU/PICU should be continued in the interventional radiology suite. Given the diminutive size of the neonate, the use of the NICU ventilator can assure more reliable and efficient ventilation during the procedure. A total intravenous anesthetic (TIVA) technique (opioid and nondepolarizing muscle relaxants) will optimize cerebral metabolic coupling while accomplishing the goal of keeping the patient immobile. Propofol at high doses may have cardiovascular depressant effects and should be administered judiciously [23]. The interventionalist will use liberal amounts of crystalloids, heparin, and contrast media as part of the procedure. Therefore, any fluids administered by the anesthesia provider need to account for the total fluid intake in order to minimize volume overload, especially in the setting of preexisting CHF. Given the technical difficulty in positioning the endovascular catheters, patient immobility is paramount. The procedure may require frequent apneas and transient cardiac arrest to aid in imaging catheter placement and angiography [50]. Embolization with ethylene vinyl alcohol copolymer glue (Onyx, Covidien, Plymouth, MN) can induce bradycardia and asystole [51]. Catastrophic vessel perforation can lead to massive blood loss, intracranial hemorrhage, and symptomatic increases in ICP. Frequently, staged partial occlusion of these pathologic vessels will be performed. Furthermore, embolization of large high-flow low-resistance arteriovenous malformation can provoke a hypertensive episode which can precipitate bleeding. Therefore, contingency plans for an emergency craniotomy for evacuation of hematoma and ligation of bleeding vessels are mandatory. A thorough preoperative anesthesia consent should include discussion of catastrophic and permanent injury, including death.

Postoperative Management

Given the prolonged nature of these endovascular procedures and the fragile cardiovascular function of these neonates, postoperative observation in an ICU setting should be routine. Often, mechanical ventilation will require sedation. Sedation should be intermittently halted in order to perform a neurological examination. These patients are still at risk for swings in blood pressure, intracranial hemorrhages, and seizures. Unpredictable hemodynamics post-embolization increase the risk for hemorrhage, especially in partial embolization procedures [52].

Ophthalmology

Neonates are susceptible to both congenital and acquired lesions that require anesthesia for ophthalmological therapy [53]. Given the vulnerability of the surgical neonate, the urgency of the surgery needs to be gauged against the risk of the anesthesia. Most of these neonates will require an examination under anesthesia/sedation (EUA). Therefore, the side effect of ophthalmic drugs and potential anesthetic interactions should be acknowledged. These interactions are delineated in Table 10.1.

Table 10.1 Eye drops commonly used in neonates and their possible complications

Drug	Action	Side effects
Cyclopentolate	Anticholinergic (similar action to atropine, but faster onset of action and shorter half-life)	Grand-mal seizure [54–56]; psychotic reactions [57–60]; gastro-intestinal toxicity [61]
Phenylephrine	Sympathomimetic/adrenergic	Hypertension
Tropicamide	Anticholinergic/para-sympatholytic	Gastro-intestinal (more pronounced in children) [62]
Atropine	Anticholinergic/para-sympatholytic (anti-muscarinic)	Tachycardia [62]; gastro-intestinal [62]; atropine flush/fever, acute confusion/psychosis
Homatropine	Anticholinergic/para-sympatholytic, similar effects to atropine but weaker	

Table 10.2 Common neonatal congenital lesions of the eye

Congenital lesion	
Coloboma	Incomplete closure of the choroid fissure
Glaucoma	Abnormal iridocorneal angle
Cataracts	Opaque lens due to infection
Detached retina	Persistence of intraretinal space
Microphthalmia	Underdeveloped small eye
Peter's anomaly	Persistent lens stalk

Congenital Ophthalmologic Lesions

Congenital lesions in the neonate primarily require sedation or general anesthesia for a complete and thorough examination of both eyes. The principles noted above and elsewhere in this book should be applied. Many of these congenital lesions may be syndromic and are mostly managed conservatively until 6 months to 1 year when the risk associated with surgery and anesthesia is reduced. Common neonatal congenital lesions are listed in Table 10.2.

Acquired Lesions

Retinopathy of Prematurity

Retinopathy of prematurity (ROP) is the most common etiology of childhood blindness and afflicts many vulnerable neonates [63]. Frequently, coexisting conditions associated with prematurity complicate the care. These include bronchopulmonary dysplasia, intraventricular hemorrhages, and necrotizing enterocolitis, all of which are life-threatening and take precedence in acute management of these patients.

All infants born at a gestational age of 30 weeks or less or with a birth weight of ≤1500 g should have serial screening for ROP. These exams may occur in the NICU but often require sedation. Early laser photocoagulation for retinal ablation has been shown to improve visual acuity [64]. These procedures require an immobile patient and general anesthesia can be managed with a variety of techniques in the operative suite or NICU [65]. However, it should be noted that most of these patients are premature and are at increased risk for postoperative apnea and bradycardia and should be monitored and managed accordingly.

Trauma

Ophthalmologic trauma in the neonate may result from nonaccidental injury [66]. These patients can present with retinal hemorrhages and increased intraocular pressure. A thorough preoperative assessment for comorbid injuries is critical. Similarly, it is important to liaise closely with general pediatrics, medical imaging, critical care, social work, and children's aide to ensure comprehensive perioperative management of the medical and non-medical issues [67]. Birth trauma can also lead to retinal hemorrhages. These occur in 26% of normal vaginal deliveries, 43% of vacuum extractions, and 52% of combined forceps and vacuum deliveries. 83% of these lesions resolved in 10 days [68].

Summary

The approach to the neonates with neurological and ophthalmological lesions is based on fundamental understanding of the surgical lesion and implications of maturational changes of the developing organ systems. Neonatal surgery is associated with increased perioperative morbidity and mortality, including persistent cognitive deficits [2, 6–8]. Therefore, a comprehensive preoperative evaluation, meticulous intraoperative care, and close postoperative observation are indicated in this vulnerable patient group.

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Cardiac Surgery

11

Wanda C. Miller-Hance, Erin A. Gottlieb, and Pablo Motta

Introduction

Cardiac surgery in the neonate is usually indicated to correct or palliate congenital malformations of the cardiovascular system. Extremely rare in this age group is the need for surgical intervention for pathologies such as endocarditis, cardiac tumors, or pericardial disease. Thus, the focus of this chapter is on anesthesia for cardiac surgery in the neonate with congenital heart disease (CHD). A brief overview of the cardiovascular physiology of the fetus and neonate is presented, followed by a discussion of CHD that includes epidemiology, clinical features, and diagnosis in the neonate. Selected anomalies of particular relevance that occur in this age group are reviewed, with emphasis on anatomic features, pathophysiology of the defect, perioperative management, and specific considerations during anesthetic care. This is followed by an in-depth discussion of pertinent aspects of anesthetic practice in the neonate with CHD undergoing cardiac surgery. Finally, several specific perioperative problems and concerns in the neonate are highlighted.

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Cardiovascular Physiology

An understanding of the important features of the fetal and neonatal circulations is essential for those who care for the neonate with heart disease. These include the differences in blood flow patterns and distribution of blood flow, changes at birth, and the transition of the circulation. Familiarity with the clinically relevant developmental aspects of cardiac physiology is key as well. The section that follows provides a brief review of our current understanding of these subjects. It should be noted that much of the data regarding the fetal circulation has been derived from studies in the fetal lamb, with the information extrapolated to the human fetus.

Types of Circulation

Fetal Circulation

The placenta is the organ of oxygen and carbon dioxide exchange between the fetus and the mother, serving the role in utero of the postnatal pulmonary system. It is also the site of nutrient uptake for the developing fetus. Oxygenated blood from the placenta reaches the fetus via a single umbilical vein. This blood has the greatest oxygen tension (pO_2) in the fetus (range, ~30 to 35 mmHg). Blood from the umbilical vein courses through the liver; the left lobe receives blood from the umbilical vein, and the right lobe receives blood from both the umbilical and portal venous systems. A majority of umbilical venous blood (~50 to 60%) bypasses the liver by midterm gestation and enters the inferior vena cava (IVC)-right atrial (RA) junction through the ductus venosus. Thus, blood in the IVC during fetal life originates from the liver, the lower body, and the placenta (via the ductus venosus). Approximately 30% of IVC blood is directed across the foramen (or fossa) ovale into the left atrium (LA) (Fig. 11.1). Preferential streaming blood flow patterns in the fetal heart direct the more oxygen-saturated blood from the umbilical vein (via the ductus venosus) and left hepatic vein to be diverted

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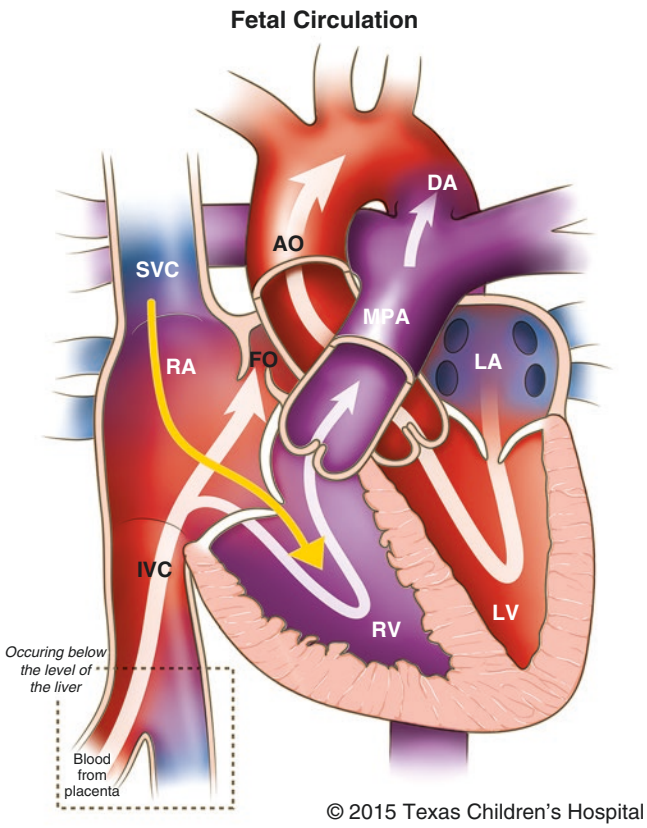

Fig. 11.1 Illustration of the circulation in the fetal heart. The oxygenated blood reaching the right atrium (RA) from the placenta via the umbilical vein and ductus venosus is preferentially shunted across the foramen ovale (FO) into the left heart. In the left atrium (LA), blood mixes with the small amount of pulmonary venous return and is ejected by the left ventricle (LV) into the aorta (AO). A portion of the oxygenated blood in the RA mixes with deoxygenated blood from the inferior (IVC) and superior vena cava (SVC) and courses into the right ventricle (RV). Most of the RV output is shunted from the main pulmonary artery (MPA) across the ductus arteriosus (DA) into the systemic circulation. Reproduced with permission from Texas Children's Hospital

into the LA across the limbus of the foramen ovale. Thus, this communication is an important site of shunting in the fetal heart. The direction of blood flow across the foramen ovale in utero is normally from the RA to the LA. In the LA, blood mixes with the small amount of pulmonary venous return and is ejected by the left ventricle (LV) into the ascending aorta (Asc Ao). This relatively "highly" oxygenated blood is distributed to the coronary arteries, cerebral circulation, and upper extremities. The remaining blood from the IVC [mostly from the lower body and liver] mixes in the RA with blood from the superior vena cava (SVC) and coronary sinus, which has a relatively low pO_2 (~12 to 14 mmHg). Mixed blood then courses across the tricuspid valve and enters the right ventricle (RV; pO_2 ~ 18 to 19 mmHg), where it is ejected into the main pulmonary artery (MPA). A state of high pulmonary vascular resistance associated with the airless collapsed lungs and fetal low pO_2 limits pulmonary blood flow, and most of the blood ejected from the RV courses through the ductus arteriosus into the descending aorta (Desc Ao). Desaturated blood from the Desc Ao reaches the placenta via the umbilical arteries. Thus, the pattern of the fetal circulation provides extremely efficient gas exchange in the placenta.

Table 11.1 Characteristic features of the fetal and neonatal circulations

Feature	Fetal circulation	Neonatal circulation
Arrangement of the circulation	In parallel	In series
Shunts	Present (essential)	Absent
Pulmonary vascular resistance	High	Low
Cardiac output	Low	High
Site of gas exchange	Placenta	Lungs

In summary, the fetal circulation is characterized by parallel circulations, the presence of intracardiac and extracardiac shunts, and an increased pulmonary vascular resistance (Table 11.1). Although CHD can be associated with hemodynamic alterations and abnormal blood flow patterns in the fetus, the presence of these shunts compensates to a great extent for these changes, ensuring survival until delivery in most cases.

The Transitional Circulation

At birth, three major changes in the circulation occur with ligation of the umbilical cord: (1) the placenta is excluded from the circulation and the lungs assume the function of gas exchange, (2) the lungs expand, greatly reducing the pulmonary vascular resistance and increasing pulmonary blood flow, and (3) systemic vascular resistance increases as the low-resistance placental vascular bed is removed, leading to an increase in LV afterload and a decrease in the volume of blood returning to the IVC. After birth, the shunts between the pulmonary and systemic circulations during fetal life [ductus venosus, foramen ovale, and ductus arteriosus] normally close. The ductus venosus usually closes within 24 h of birth. The mechanisms involved in this process are incompletely understood, but believed to rely primarily on a passive process. Postnatal functional closure of the foramen ovale occurs when the LA pressure exceeds the RA pressure. LA pressure increases as a consequence of the marked augmentation of the pulmonary venous return associated with the increased pulmonary blood flow. RA pressure decreases in parallel with the concomitant decrease in IVC pressure/flow. Patency of the foramen ovale facilitates shunting at the atrial level, the direction of which depends on the relative atrial pressures and other factors. It is not unusual for occasional right-to-left shunting or bidirectional shunting to occur across the foramen during the first few hours or days after birth; this normally has no hemodynamic consequence. A change in

the direction of shunting across the ductus arteriosus occurs from right to left in fetal life to left-to-right in postnatal life. This change in the direction of the flow provides the ductus arteriosus with blood with a greater pO_2, which stimulates closure of this communication. Constriction of the ductus arteriosus is attributed to a local effect of the increased pO_2 plus a reduction in the plasma concentrations of circulating prostaglandins that ensues at birth. Functional closure of the ductus arteriosus occurs within 10–25 h after birth, whereas complete obliteration of the ductal lumen occurs within the first few weeks after birth [1]. If the normal increase in the arterial pO_2 does not occur because of either pulmonary or cardiac disease, or the constrictor response to oxygen is diminished (i.e., prematurity), the ductus arteriosus may remain patent.

It is important to recognize that the changes that take place at birth, which are essential to normal physiology, may significantly compromise the circulation of the neonate with a congenitally malformed cardiovascular system [2]. Limited or lack of shunting across anatomic fetal structures in the neonate with CHD postnatally, for example, can be catastrophic unless and until these communications are re-established.

Postnatal Circulation

In the neonate, the adult pattern of blood flow through the heart is established; RV output (pulmonary blood flow) and LV output [systemic blood flow] are equal, and, normally, no shunts are present. In summary, in contrast to that of the fetus, the circulation in the neonate operates in series, lacks shunts, and is characterized by a progressive decrease in pulmonary vascular resistance (Table 11.1).

Cardiac Output and Distribution of Blood Flow

In the fetus, both the RV and the LV eject blood into the systemic circulation; thus, the cardiac output of the two ventricles is in parallel. The total volume of blood ejected by both ventricles in the fetus is referred to as the combined ventricular output (CVO). The RV contributes two-thirds of the CVO, whereas the LV ejects only one-third. A small amount of the CVO, in the range of 5% to 10%, reaches the pulmonary circulation, and 55% to 60% courses through the ductus arteriosus into the Desc Ao. Approximately 3% of the CVO reaches the heart and 22% the upper body. Only 10% of the CVO courses through the Ao arch isthmus into the Desc Ao. Throughout gestation, a gradual reduction occurs in the fraction of CVO that is distributed to the placenta as the ventricular output increases to meet the increased demands of developing fetal organs [3]. Cardiac output increases immediately after birth to meet the metabolic requirements of the neonate, with associated significant increases in blood flow to the lungs, kidneys, and gastrointestinal system; the LV output increases to approximate that of the RV.

Developmental Aspects of the Myocardium

The fetal myocardium is structurally and functionally immature and has limited potential to increase cardiac output [4]. These features are suited to a low-pressure system with a low systemic vascular resistance. The main energy substrates for the fetal heart are lactate and glucose. As the mitochondria mature, the energy substrates transition from carbohydrates to fatty acids [5].

The ultrastructure of the neonatal myocardium is poorly organized. The neonatal heart has fewer myocytes, the arrangement of the myofibrils is relatively poor, and the proportion of contractile elements is less than those in the adult myocardium [6]. In essence, the neonatal heart operates with an incompletely developed contractile system. Additional characteristics of the neonatal myocardium include: (1) control of contractility depends to a greater extent on circulating catecholamines and adrenal function than on direct autonomic influences, (2) the sarcoplasmic reticulum, the primary source of calcium storage for excitation-contraction coupling, is poorly developed, and (3) a deficiency in T tubules results in a significant dependence on transmembrane calcium fluxes. Thus, the neonatal heart is ill-equipped to increase contractility in the face of an increased demand.

Other properties of the neonatal myocardium that limit its ability to augment cardiac output include: (1) less compliant ventricles that are less able to increase stroke volume, resulting in a greater dependence upon the heart rate to increase cardiac output, (2) limited tolerance to changes in preload secondary to less ability to recruit the Frank-Starling mechanism, (3) less ability to significantly increase the contractile state, and (4) poor compensation for changes in afterload. An important aspect of neonatal cardiac function is the ventricular interdependence. Failure of one ventricle will impact the filling and hence the function of the other. These characteristics dictate some of the important principles of perioperative neonatal cardiac management including the frequent indication for inotropic support, the value of calcium boluses or infusions, and the use of cardiac pacing. These characteristics also explain the greater sensitivity of the neonatal myocardium to anesthetic drugs [7]. The major differences between the neonatal and adult myocardium are summarized in Table 11.2.

Postnatal cardiac development is accompanied by the loss of fetal regenerative capacity of cardiomyocytes within the first few days after birth. The loss of fetal hyperplastic growth is replaced with postnatal hypertrophic growth of the myocardium. The mechanism for this loss in regenerative capacity is incompletely understood in humans and widely variable

Table 11.2 Summary of major differences between neonatal and mature myocardium

Parameters	Neonatal heart	Mature heart
Physiology		
Contractility	Limited	Normal
Heart rate dependence	High	Low
Contractile reserve	Low	High
Preload tolerance	Limited	Better
Afterload tolerance	Low	High
Ventricular interdependence	Significant	Less
Ca^{++} handling		
Predominant site of Ca^{++} flux	Sarcolemma	Sarcoplasmic reticulum
Dependence on normal iCa^{++}	High	Lower
Circulating catecholamines	High	Lower
Adrenergic receptors	Downregulated insensitive β_2, β_1 predominant	Normal β_1 predominant
Innervation	Parasympathetic predominates; sympathetic incomplete	Complete
Cytoskeleton	High collagen and water content	Lower collagen and water content
Cellular elements	Incomplete SR, disorganized myofibrils	Mature SR, organized myofibrils

Ca++ calcium, *iCa++* ionized calcium, *SR* sarcoplasmic reticulum
From Andropoulos DB, Yuki K, and Koutsogiannaki S. Physiology and cellular biology of the developing circulation. In Andropoulos DB, Mossad EB, and Gottlieb EA editors. *Anesthesia for Congenital Heart Disease*, fourth Ed, Hoboken: Wiley-Blackwell; 2023; with permission

among large animal models. There is emerging evidence that the cardiac microenvironment transforms with changes in the extracellular matrix composition associated with the development of the immune system [5]. The ability to arrest the decline in the capacity for regeneration would open potential therapies for neonatal CHD [8].

Epidemiology of Congenital Heart Disease

CHD is the most common birth defect in humans. In the USA CHD affects approximately 8 out of 1000 live births (Table 11.3) [9]. The worldwide prevalence of CHD has increased substantially over time, from <1 per 1000 live births in 1930 to 9 per 1000 live births in recent decades, corresponding to 1.35 million worldwide live births affected with CHD every year [10]. The prevalence may be even greater than previously thought as a study in a large cohort of neonates undergoing echocardiographic screening revealed a live birth prevalence of CHD of 26.6 per 1000 [11]. The reported birth prevalence of CHD globally is increasing steadily due to the availability of diagnostic techniques in lower-income countries. Interestingly, for simple lesions (e.g., septal defects) the prevalence is increasing possibly due to improved diagnosis. In contrast, the birth prevalence of complex left-sided obstructive lesions (e.g., hypoplastic left ventricle) is decreasing, probably due to diagnosis in utero and, in industrialized countries, the decision to terminate the pregnancy [12].

Table 11.3 Annual birth prevalence of congenital cardiovascular defects in the USA

Type of presentation	Rate per 1000 live births	Estimated number (variable with yearly birth rate)
Fetal loss	Unknown	Unknown
Invasive procedure during the first year	2.4	9200
Detected during the first year[a]	8	36,000
Bicuspid aortic valve	13.7	54,800

From Benjamin et al. [9], with permission
[a] Includes stillbirths and pregnancy termination at < 20 weeks of gestation; includes some defects that resolve spontaneously or do not require treatment

To further complicate the epidemiology of CHD in neonates, large regional variations in the prevalence have been reported [13]. The prevalence of CHD in preterm infants is twice that in infants born at full term [14]. Approximately 16% of infants presenting with CHD were premature at birth. Updated epidemiological data suggest that 20–30% of CHD has an identifiable underlying etiology, with the proportion of CHD attributable to single gene disorders of 3–5%, chromosomal anomalies of 8–10%, and pathogenic deletions/duplications of 3–25% [15]. CHD may also be associated with a genetic pattern of inheritance (10%) (e.g., trisomy 18, 21, 4p deletion, and 22q11 deletion) and epigenetic and/or a syndromic pattern (as in omphalocele and Holt-Oram syndrome) [15]. Maternal rubella infection is also known to predispose the fetus to CHD.

The predominant cause of death in the first year of life is CHD [16]. Without treatment, the condition is fatal in a substantive number of neonates, with increased mortality observed in preterm infants [14]. Twenty-five percent of infants with CHD require intervention in the first year of life in order to limit mortality [17]. Neonates account for ~17–22% of patients included in the Society of Thoracic Surgeons Congenital Heart Surgery Database who undergo cardiothoracic surgical interventions each year (7,531 of 33,513 patients as per report of the period ending 06/30/2022, mostly from North American Centers). This fact emphasizes the need to appreciate the considerations for anesthesia care for neonates who require cardiac surgery.

Despite many advances in the care of neonates with CHD, a number of factors including the late detection of critical pathology contribute to the early morbidity and mortality in these infants. In an effort to address this increasing problem and to improve the early diagnosis of critical CHD in the neonate, pulse oximetry (SpO_2) has been adopted in several countries, including the USA [18–21]. Mandatory policies for such screening

have been introduced in some states before it was adopted nationwide. This resulted in a significant decrease in infant cardiac deaths between 2007 and 2013 in the states that adopted such screening compared with those without these policies [22].

The pulse oximetry screening recommendation of the American Academy of Pediatrics (AAP) for critical CHD is to measure the oxygen saturation after 24 h of age on both their right hand and one foot simultaneously. Criteria suggestive of CHD include any one of the following: (1) oxygen saturation of <95% in both extremities on three serial measurements, (2) saturation is ≤90% in either extremity, or (3) a difference between the saturations of ≥3% [23]. It should be recognized that neonates with a negative screen may still have critical CHD due to the fact that hypoxemia may only be present intermittently in some defects.

Clinical Presentation and Diagnosis of Congenital Heart Disease in the Neonate

The presentation of CHD in the neonate depends upon the nature and severity of the pathologic abnormalities [24]. Although in many cases CHD is detected during fetal ultrasound screening or immediately after birth, in some instances the diagnosis is made at a later age. A particularly ominous presentation is that of the apparently healthy neonate who develops life-threatening symptoms after discharge from the nursery, requiring urgent medical attention. Early recognition and appropriate management of the infant with critical CHD are essential to optimize outcome.

The neonate with significant CHD varies in his/her clinical manifestations from no signs or symptoms immediately after birth to the gradual onset of signs or symptoms as their physiology changes (i.e., ductus arteriosus closure, alterations in pulmonary vascular tone). The most common clinical features of CHD in the neonate are respiratory distress, cyanosis, a heart murmur, and signs of reduced cardiac output [24]. Respiratory distress (i.e., tachypnea, labored breathing, intercostal retractions) is usually associated with defects that result in an increase in LA volume/pressure. These symptoms may reflect pulmonary over-circulation (left-to-right shunts), obstructed pulmonary venous drainage, or pathology that leads to an increase in LV end-diastolic volume/pressure. Clinical cyanosis is usually apparent when the concentration of reduced hemoglobin exceeds 5 g/dL. Although often due to lung disease, cyanosis may also indicate cardiac disease secondary to reduced pulmonary blood flow, right-to-left shunting, or a mixing physiology. The presence of a heart murmur in the neonate is sometimes, but not always, associated with CHD. Conversely, serious CHD can be present in the absence of a murmur. Hypotension may indicate impending or frank hemodynamic decompensation and often implies serious cardiac pathology that requires immediate intervention to stabilize the infant and prevent vital organ damage.

In the neonate with suspected CHD, the physical examination should include four extremity blood pressure determinations and pre- and post-ductal SpO_2 measurements. A hyperoxia test may be performed in an effort to distinguish cardiac disease from other causes of cyanosis. This consists of the sequential administration of room air or 100% oxygen while measuring the arterial oxygen tension (PaO_2) in the right radial artery (pre-ductal site) and in a lower extremity/umbilical artery (post-ductal site). If the cyanosis is related to pulmonary disease, supplemental oxygen should increase the PaO_2 > 150 mmHg. In contrast, if the cyanosis is related to CHD, supplemental oxygen will have little or no effect on the PaO_2, the value remaining <100 mmHg. This response in the neonate with CHD is referred to as failure of the hyperoxia test. Additional studies such as a chest radiograph and a complete electrocardiogram that includes right-sided chest leads (V3R and V4R), and in some cases a posterior chest lead (V7), are routinely obtained. Echocardiography is the primary imaging modality for the initial evaluation and serial assessment of most types of CHD. It is diagnostic in most neonates. In only rare cases are additional studies such as chest computed tomography, cardiac magnetic resonance, or cardiac catheterization and angiography required to further delineate the anatomical or functional abnormalities.

Classification of Congenital Heart Disease

Numerous classification schemes have been proposed for CHD [25, 26]. These categorize malformations based on (1) complexity of the lesion as simple versus complex disease, (2) presence or absence of cyanosis, (3) whether pulmonary blood flow is increased or decreased, (4) whether an obstruction is present affecting the RV or LV, and (5) the direction of shunting patterns (i.e., left-to-right, right-to-left). Other classification systems are based on the underlying physiologic alterations or common features of the anomalies. An alternate approach that facilitates a differential diagnosis in the neonate with CHD considers the clinical presentation and categorizes defects based on the presence of cyanosis, congestive heart failure, or a heart murmur [27]. Yet a third scheme relevant to neonatal screening for CHD suggests three main categories in terms of clinical significance as follows [28]:

- Life-threatening congenital heart defects: those in which cardiovascular decompensation or collapse is likely (e.g., transposition of the great arteries, coarctation/interrupted aortic arch, aortic stenosis, pulmonary atresia, and hypoplastic left heart/mitral atresia).
- Clinically significant congenital heart defects: those with effects on heart function but where collapse is unlikely (e.g., ventricular septal defect, complete atrioventricular septal defect, atrial septal defect, tetralogy of Fallot).

- Clinically insignificant congenital heart defects: those with no functional clinical significance (e.g., small ventricular septal defect only detectable by echocardiography and requiring no treatment).

This third categorization is useful for determining the gravity of the situation and the immediate action needed once the diagnosis is made. Life-threatening lesions, often because of ductal dependency for pulmonary or systemic blood flow or other reasons, require prompt attention (Table 11.4). Clinically significant CHD, although important, may not present with major hemodynamic manifestations within the first few weeks of life and is less likely to necessitate urgent care. Defects considered clinically insignificant have little to no potential of impacting the physiology in the neonate.

Although any cataloging system has limitations, a pathophysiologic classification is particularly helpful in the practice of anesthesia, as it allows for the formulation of hemodynamic goals based on the main consequences of the defect. One such classification system of CHD is presented in Table 11.5 [29].

Table 11.4 Ductal-dependent congenital heart disease in the neonate

Ductal-dependent lesions for pulmonary blood flow	Ductal-dependent lesions for systemic blood flow
Critical pulmonary stenosis	Coarctation of the aorta
Pulmonary atresia with intact ventricular septum	Critical aortic stenosis
Complex lesions associated with severe pulmonary outflow tract obstruction or pulmonary atresia	Hypoplastic left heart syndrome
Severe form of Ebstein anomaly with anatomic or functional pulmonary atresia	Interrupted aortic arch
d-Transposition of the great arteries[a]	Complex lesions associated with systemic outflow tract obstruction or aortic atresia

[a] Patency of the ductus arteriosus in *d*-transposition increases pulmonary blood flow and augments pulmonary venous return, leading to stretching of the interatrial communication and enhancing intercirculatory mixing

Table 11.5 Physiologic classification of congenital heart defects and respective salient features

Lesions characterized by volume overload
• Due to communications at the atrial, ventricular, and/or arterial level.
• Frequently the result of physiologic left-to-right shunting.
• If the communication is proximal to the mitral valve (e.g., atrial septal defect, partial anomalous pulmonary venous return, or unobstructed total anomalous pulmonary venous return), right heart dilation is present; if the shunt is distal to the mitral valve (e.g., ventricular septal defect, patent ductus arteriosus), dilation of left-sided cardiac structures is seen.
• Symptoms related to the magnitude of the shunt and pulmonary to systemic blood flow ratio.
• Shunting influenced by the pulmonary vascular tone and relationships between the pulmonary and systemic vascular resistances.
• Diuretic therapy and, in some cases, afterload reduction are main medical management strategies.
Lesions characterized by obstruction to systemic blood flow
• Include those with ductal-dependent systemic blood flow (e.g., critical aortic stenosis, severe aortic coarctation, aortic arch interruption, hypoplastic left heart syndrome, aortic atresia).
• Prostaglandin E_1 therapy required to maintain ductal patency allowing for systemic blood flow until an intervention is undertaken.
• Diuretic therapy and manipulation of the systemic and pulmonary vascular resistances may be required to control increased pulmonary blood flow and optimize systemic output.
• Inotropic and/or mechanical ventilatory support frequently necessary.
Lesions characterized by obstruction to pulmonary blood flow
• Include those with ductal-dependent pulmonary blood flow (e.g., critical pulmonary valve stenosis and pulmonary atresia with intact ventricular septum).
• Prostaglandin E_1 therapy is indicated for the treatment of arterial hypoxemia until obstruction can be relieved or alternate sources of pulmonary blood flow are established.
Parallel circulation
• Classic lesion is that of *d*-transposition of the great arteries where the pulmonary and systemic circulations run in parallel.
• Associated with cyanosis.
• Intercirculatory mixing is essential for survival.
Single ventricle lesions
• Include those with atrioventricular valve atresia (e.g., tricuspid atresia), severe ventricular hypoplasia (e.g., hypoplastic left heart syndrome), or anomalies where a biventricular repair is not feasible (e.g., unbalanced atrioventricular septal defect, double inlet left ventricle).
• Common among these lesions is complete mixing of the systemic and pulmonary venous blood at the atrial or ventricular level, and aortic or pulmonary outflow tract obstruction, accounting for the presence of cyanosis.
• An important goal of early management involves optimization of the balance between the pulmonary and systemic circulations.

Congenital Cardiovascular Anomalies of the Neonate: Anatomy, Pathophysiology, and Management, with Anesthetic Considerations

The remarkable advances in perioperative care during the last several decades have refined congenital heart surgery in the neonate, resulting in increased survival rates and greatly improved outcomes [30]. These advances have permitted new approaches for many defects: early corrective surgery now being preferred over initial palliation and later repair. The rationale for early correction is based on the premise that by restoring the anatomy and physiology towards normal early in life, subsequent morbidity can be minimized, allowing for the most favorable long-term outcomes. As a result, the volume of corrective surgery during the neonatal period has markedly increased. The section that follows addresses selected congenital cardiovascular defects reviewing relevant aspects of the anatomy and physiology, highlighting pertinent medical and surgical management, and focusing on considerations regarding anesthesia care.

Patent Ductus Arteriosus

Anatomic Features

The ductus arteriosus is a vascular communication between the MPA and the Desc Ao (Fig. 11.2). This structure is an essential component of fetal life, serving as a conduit to direct RV output into the Desc Ao. In some cases, the ductus arteriosus fails to close after birth, resulting in persistent patency. Prematurity and respiratory distress syndrome are risk factors for persistent patency known as patent ductus arteriosus (PDA). This lesion affects nearly a 33% of infants <1500 grams at birth. A PDA occurs with increased frequency in certain genetic disorders (e.g., Holt-Oram syndrome), in association with in utero viral infections [Rubella] and maternal drug ingestion (sodium valproate) [1].

A PDA can be found in isolation or in association with other forms of CHD. In the isolated form, it accounts for nearly 10% of all congenital heart defects. In some cardiovascular malformations, ductal patency may be essential for either pulmonary or systemic blood flow and, therefore, neonatal survival. The discussion that follows addresses the isolated defect.

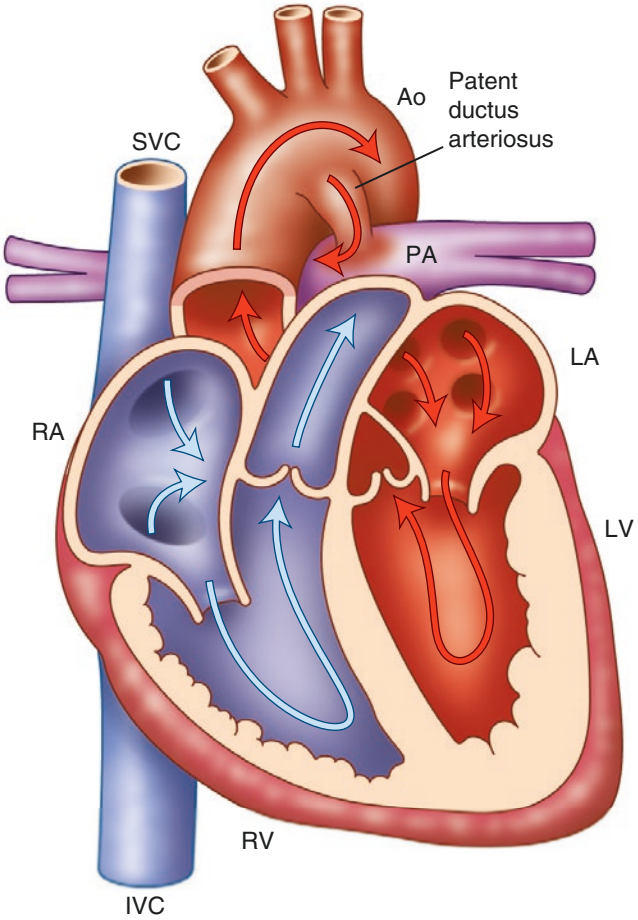

Fig. 11.2 Graphic representation of a patent ductus arteriosus. The communication between the aorta (Ao) and pulmonary artery (PA) is shown. The usual direction of shunting, from left-to-right, in the isolated lesion is noted. *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

Pathophysiology

Communication at the level of the great arteries permits shunting between the systemic and pulmonary circulations. Two factors determine the direction and magnitude of the shunting: the relative resistances of the pulmonary and systemic vascular beds and the size of the communication. The pulmonary vascular resistance significantly affects the direction of shunting. As the resistance decreases postnatally, the typical direction of blood flow through an isolated PDA is left-to-right, resulting in increased pulmonary blood flow and volume loading of the heart.

The clinical manifestations of a PDA depend on the magnitude of the shunt and the cardiopulmonary responses to the shunt. Some ductal communications are restrictive (small diameter) in nature and limit the blood flow to some extent. Other more sizeable communications permit a substantial amount of blood flow from the Ao to the PA. In the latter case, the neonate may develop signs of pulmonary over-circulation (tachypnea, labored breathing, radiographic evidence of increased interstitial lung water, LA/LV dilation, cardiomegaly) and overt congestive heart failure. The preterm neonate is particularly vulnerable to the hemodynamic effects of a left-to-right shunt, which can lead to pulmonary edema [31]. Frequently, a hemodynamically significant PDA is associated with respiratory impairment, a requirement for mechanical ventilatory support, and/or failure to wean from the ventilator. A PDA in the preterm infant is considered a risk factor for complications such as bronchopulmonary dysplasia, necrotizing enterocolitis, and intracranial hemorrhage. The diastolic runoff (left-to-right shunt), also called pulmonary steal, can cause hypoperfusion of systemic vascular beds leading to end-organ dysfunction (i.e., impaired myocardial perfusion, gut ischemia, renal injury) [32]. The lack of significant ductal restriction and the increased pulmonary blood flow leads to pulmonary hypertension, imposing a further pressure load on the RV.

Management

The goals of medical therapy are designed to control pulmonary over-circulation and ventricular volume overload. In most cases, this includes supportive treatment, which consists of fluid restriction and diuretic therapy [33]. The administration of indomethacin or ibuprofen to promote ductal closure in the preterm infant in clinical practice is well-established [34]. In a recent multicenter, randomized study, paracetamol was less effective than ibuprofen to close the ductus arteriosus (52% versus 78%), although the constriction rate and the need for surgical closure of the ductus with the two drugs were similar [35]. Pharmacological therapy to close a patent ductus may be less successful in very low-birth-weight infants. Non-steroidal anti-inflammatory agents may also be contraindicated due to side effects affecting renal, gastrointestinal, and cerebral perfusion. Ongoing debate continues regarding the management of a PDA in extremely preterm infants [36, 37]. A percutaneous catheter-based procedure to occlude the PDA is an option in some infants and this type of approach has been used even in extremely preterm neonates [38–40]. The experience thus far using an approved device for ductal closure in preterm neonates appears encouraging [41]. Surgical therapy of a PDA in the neonate usually consists of placing a clip or ligature around the communication, most commonly via a small posterior lateral thoracotomy [42]. Although ductal closure using video-assisted thoracoscopy has been reported in the neonate and even in preterm infants, this approach is more likely to be considered in the older infant or child [43, 44]. It is of interest that very low-birth-weight infants who had percutaneous catheter closure of their PDA did not experience post-ligation syndrome (see below) and had less escalation of respiratory support compared with infants who underwent surgical ligation [45].

Anesthetic Considerations

The need for intervention in the full-term neonate for a hemodynamically significant PDA is quite unusual and is more likely to occur if other coexisting disease is present. Infants undergoing transcatheter closure may be at risk for vascular injury, rhythm disturbances, and hemodynamic instability. These problems result from factors such as difficulty with vascular access, catheter manipulations, or blood loss. Other procedural complications include device embolization and/or malposition. In the neonate undergoing surgical ductal ligation, standard anesthetic practice for thoracotomy procedures in the small infant should be followed. The use of regional anesthesia techniques can contribute to perioperative pain management as discussed in a later section.

If the preterm infant requires surgical closure, a left thoracotomy is performed in the neonatal intensive care unit (NICU) in many centers. This avoids the need to transport the critically ill neonate to the operating room, thereby decreasing the risk of problems such as hypothermia and accidental tracheal extubation. This approach is particularly useful if the infant requires high-frequency oscillating ventilation. An opioid-muscle relaxant-based intravenous anesthetic technique is the most common practice.

Specific Issues

- *Intravascular volume*. Fluid restriction and diuretic therapy in the neonate with a PDA deplete the intravascular volume in the presence of congestive symptoms. This problem alone or in combination with surgical manipulations that impair ventricular filling can predispose the infant to hemodynamic instability during the surgical procedure, necessitating intravenous fluid administration or other acute interventions.
- *Ventilation*. Ductal ligation requires manual manipulation of thoracic structures and retraction of the non-dependent lung to achieve optimal surgical exposure. These maneuvers can further impair gas exchange. Therefore, vigilance is of outmost importance combined with monitoring of the arterial saturation measured by SpO_2 continuously and assiduously. Preoperative placement of additional "reserve" oximetry probes should be considered. End-tidal CO_2 monitoring, routinely used in the operating room setting, may also be available for use if the surgical procedure takes place in the NICU. Adjustments to the ventilatory parameters, guided by variables being monitored to optimize gas exchange, may be necessary.
- *Pulmonary blood flow*. An important hemodynamic objective before surgical ligation of the PDA is to minimize fur-

ther increases in pulmonary blood flow that can compromise systemic output or myocardial function. Although limiting the inspired oxygen concentration is desirable in this instance, in addition to the concern of the risk of retinopathy of prematurity, this objective should be balanced with that of providing adequate systemic oxygen delivery during the procedure (see Chaps. 2 and 17) [46].

- *Blood loss*. Even a small amount of blood loss can have a major hemodynamic impact in the preterm or term neonate due to their relatively small blood volume. Thus, as in any major vascular surgery, appropriate vascular access and immediate availability of blood products are imperative. Blood loss is usually minimal, but life-threatening hemorrhage can occur.
- *Anemia*. Many preterm neonates have underlying anemia, which increases the risk of congestive heart failure. Red cell transfusion to correct anemia will significantly improve the cardiac status in many cases. Blood should be readily available during surgical ligation, regardless of site where the procedure is being undertaken. The need for preoperative red cell transfusion should be considered in anemic neonates to increase the margin of safety of the procedure.
- *Inadvertent ligation of other structures*. Unintentional ligation of adjacent thoracic structures such as the left pulmonary artery (LPA), left mainstem bronchus, and Desc Ao represents potential complications associated with ductal ligation. Pre-ductal (right upper extremity) and post-ductal (lower extremity) monitoring with a SpO_2/blood pressure cuff may allow for early recognition of complications. Ductal closure should narrow the pulse pressure and increase the diastolic and frequently, the systolic blood pressures. Confirmation of these changes during ductal ligation is reassuring.
- *Postoperative problems*. Other important issues potentially associated with ductal ligation deserve mention. If a significant pneumothorax develops, it can be catastrophic. Another concern is the possibility of nerve injury and related morbidity. The recurrent laryngeal nerve courses around the ductus arteriosus and can be injured during the procedure, resulting in vocal cord paralysis. Diaphragmatic paralysis secondary to phrenic nerve injury leading to ventilator dependency also has been reported [47]. Chylothorax due to thoracic duct injury is a rare complication. Other concerns after ductal ligation in the preterm infant relate to the effects of obliteration of the left-to-right shunt on cardiopulmonary function. In some cases, the acute increase in LV afterload can significantly compromise myocardial performance, particularly in the presence of preexisting ventricular dysfunction, which can manifest as a low cardiac output state and hypotension [31, 48, 49]. This is referred to as post-ligation cardiac syndrome. A similar picture of transient ventricular dysfunction can be seen following transcatheter closure. In some neonates, there may be an immediate need for increased mechanical ventilatory support due to sudden decreases in pulmonary compliance after surgical ligation [50].

Coarctation of the Aorta

Anatomic Features

Coarctation of the aorta (CoA) represents 5% to 8% of all congenital cardiovascular defects. The anomaly is characterized by narrowing of the lumen of the thoracic Ao near the region of the ductus arteriosus or ligamentum, resulting in obstruction to the systemic blood flow. The constriction can be discrete [Fig. 11.3] or diffuse. In the neonate, this lesion can be part of a complex disease with hypoplasia of the transverse Ao arch and isthmus (anatomic region between the left subclavian artery and aortic end of the ductus arteriosus) [51]. This constellation of findings is uncommon in older infancy or later life.

Associated pathology in CoA may include a PDA, bicuspid Ao valve, aortic stenosis (AS), subaortic obstruction, and

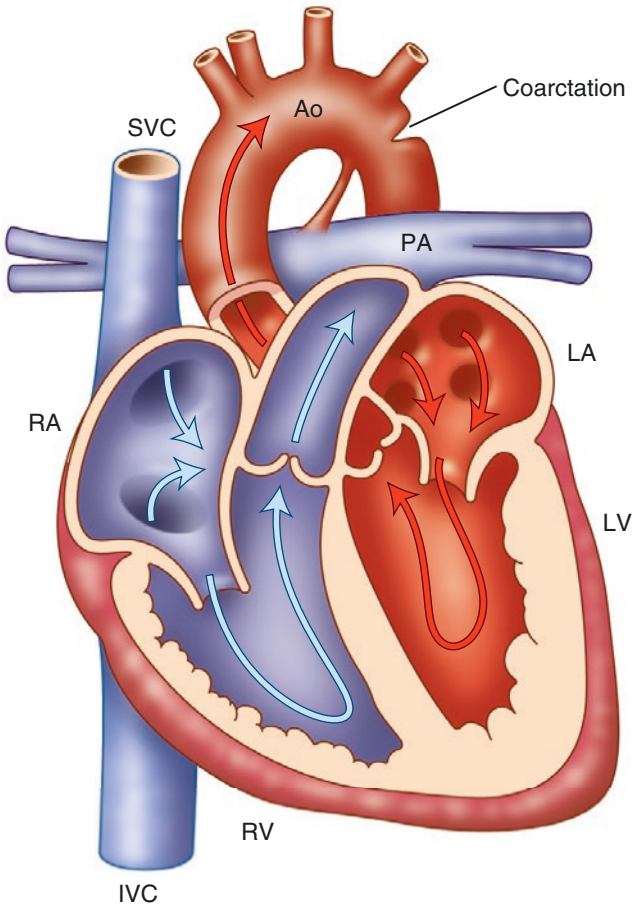

Fig. 11.3 Graphic representation of a discrete aortic coarctation. The posterior shelf in the descending thoracic aorta (Ao) in this lesion is shown. *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

ventricular septal defect (VSD). Aortic coarctation also can be one of the defects present in the Shone complex, in addition to subaortic obstruction, parachute mitral valve, and supravalvar mitral ring [52].

Pathophysiology

This lesion varies in severity, as is the case in many other forms of CHD. Presentation in a neonate usually implies more severe obstruction or the presence of coexisting anomalies [53]. The hemodynamic consequences of CoA result from the obstruction of the systemic blood flow and inadequate distal perfusion. When the PDA provides most or essentially all of the entire distal systemic perfusion via the RV, CoA is a ductal-dependent lesion for systemic blood flow. Constriction of the ductus arteriosus will have profound repercussions in this setting. In the case of less severe obstruction, ductal closure increases LV afterload and end-diastolic pressure and increases myocardial work and wall tension, which may lead to myocardial ischemia. Increased LA pressures can lead to left-to-right shunting at the atrial level and increased pulmonary blood flow. Pulmonary hypertension results from increased pulmonary venous pressures related to LA hypertension and from the increased pulmonary blood flow. Coexistent defects can also contribute to the volume or pressure load on the ventricular myocardium.

Management

Neonates with severe obstruction frequently require treatment for congestive heart failure and possible ventricular dysfunction. If poor cardiac output as manifested by decreased peripheral perfusion, metabolic acidosis, lactic acidemia, renal insufficiency, poor ventricular function, or shock is present, the situation is more ominous. This situation requires immediate intervention with tracheal intubation and mechanical ventilation in addition to prostaglandin E1 [PGE_1] therapy to re-establish/maintain ductal patency and improve systemic perfusion. Additional care may include inotropic support and, potentially, cautious afterload reduction. In most cases of moderate to severe aortic narrowing, surgical relief of the obstruction is the treatment of choice. Selection of the surgical approach, median sternotomy versus lateral thoracotomy (discussed later in the chapter), is influenced by the associated pathology, particularly the presence of aortic arch hypoplasia. The goal of the surgical procedure, regardless of the details of the specific technique or approach, is to resect the narrowed segment and remove adjacent ductal tissue. This can be part of the pathology and carries the potential for recurrence of the obstruction. Aortic continuity is preferably established by using native tissue. Associated significant Ao arch hypoplasia requires more extensive reconstruction.

Catheter-directed endovascular balloon dilation to reverse a segment of arterial narrowing as in CoA has been performed in the neonate, even in those with significant transverse arch hypoplasia [54]. Percutaneous stent placement (using a coronary artery stent) has been demonstrated to be a feasible bridging therapy in infants <1500 grams [55]. However, surgical treatment yields better immediate and midterm results compared with balloon angioplasty. The former is the preferred intervention in most centers [56].

Anesthetic Considerations

Adequate vascular access is essential. Ao cross-clamping may cause acidosis and end-organ dysfunction (spinal cord, kidneys, gut) due to hypoperfusion. This concern is greater in the neonate than in older children because of the lack of time to develop collateral circulation. Several strategies have been applied in the neonate to minimize the potential for spinal cord injury. Passive cooling or inducing mild hypothermia to 34–35 °C before applying the Ao clamp is utilized at some centers. However, the incidence of spinal cord injury in the absence of intraoperative hyperthermia is exceedingly rare [57]. Hemodynamic changes during CoA surgery via thoracotomy include hypertension upon application of the Ao cross-clamp and hypotension associated with its release. Paradoxical or rebound hypertension may occur after the repair is complete and neonatal coarctation may be followed by hypertension in later life. This latter problem has been linked to altered baroreceptor responses and abnormalities in the renin-angiotensin system [58]. Data also suggest that underlying pathological adjustment of autonomic cardiovascular homeostasis occurs in these infants [59].

Specific Issues

- *Arterial pressure monitoring*. The selection of monitors (sites and types) varies according to the surgical plan and specific approach (e.g., lateral thoracotomy versus median sternotomy; resection with end-to-end repair, extended Ao arch repair, Ao arch advancement, and the need for cardiopulmonary bypass (CPB)). Monitoring blood pressure during these cases is critical. Right radial artery pressure is standard practice although monitoring of arterial blood pressure at sites proximal and distal to the obstruction may also be considered. Additionally, monitoring blood pressure in a lower extremity using a blood pressure cuff or intravascular cannula is also common.
- *Cerebral oximetry monitoring*. Monitoring cerebral oxygenation using bilateral near-infrared spectroscopy (NIRS) may assess the adequacy of brain perfusion during the procedure and confirm a satisfactory aortic clamp position [60]. The left carotid artery might be occluded

during the period of cross-clamp [61]. Occasionally, the position of the cross-clamp can also affect flow to the innominate artery. The latter can be detected by an attenuated tracing of the right radial arterial line or right-sided NIRS monitoring. A NIRS probe over the flank region can be used as a somatic monitor to assess regional oxygenation distal to the aortic clamp [60].

- *Surgical considerations*. As Ao arch hypoplasia requires more extensive reconstruction to ensure the best long-term outcome, CPB is often required and may include the use of special bypass techniques (e.g., antegrade cerebral perfusion or ACP). If so, additional monitors (e.g., neuromonitors) may enhance the safety of the procedure.

d-Transposition of the Great Arteries

Anatomic Features

d-Transposition of the great arteries (*d*-TGA) accounts for 6% of all CHD. This malformation is identified in 10% of neonates with critical heart disease and is the most common cause of cardiac cyanosis during the neonatal period. Male infants are more commonly affected.

In *d*-transposition, the Ao arises from the anatomic RV and the PA from the LV (Figs. 11.4). In most cases, the Ao is situated anterior and to the right of the PA, in contrast to the normal position posterior to the PA. This malformation is thought to result from abnormal rotation and septation of the conotruncus, resulting in discordant ventriculoarterial connections.

In the most common form of the defect, an intact ventricular septum or a very small VSD is present (Fig. 11.5a). *d*-Transposition is associated with a larger VSD in 10% to 25% of cases (Fig. 11.5b). In complex forms of transposition, a large VSD and various degrees of pulmonary stenosis (PS) or left ventricular outflow tract (LVOT) obstruction is seen (Fig. 11.5c). Other anomalies include additional VSDs, coronary artery variants, and Ao arch obstruction.

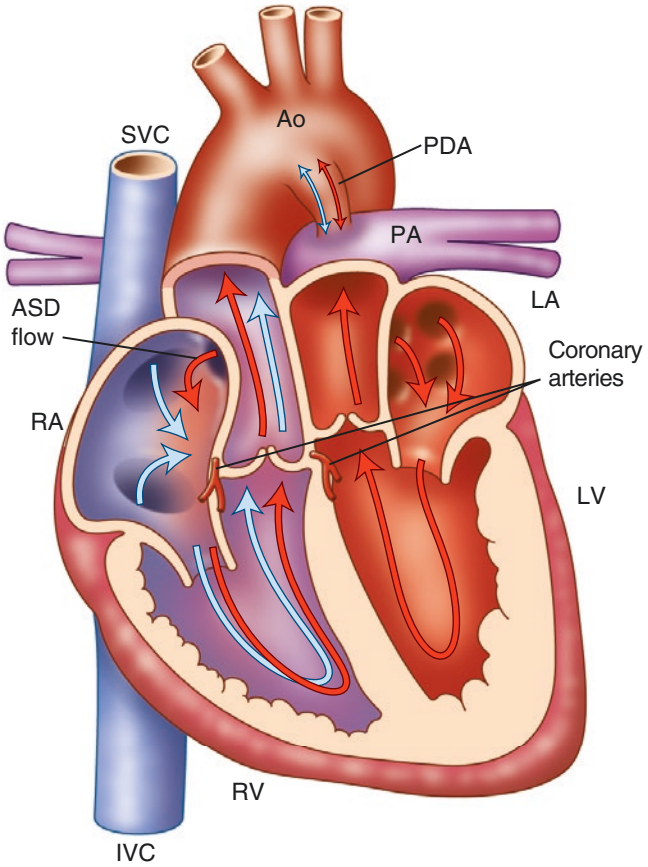

Fig. 11.4 Graphic representation of *d*-transposition of the great arteries. Intercirculatory mixing occurs at the levels of an atrial septal defect (ASD) and/or patent ductus arteriosus (PDA). The discordant connections between the ventricles and great arteries in this lesion are depicted—the right ventricle (RV) ejects into the aorta (Ao) and the left ventricle (LV) into the pulmonary artery (PA). *IVC* inferior vena cava, *LA* left atrium, *RA* right atrium, *SVC* superior vena cava

Pathophysiology

In *d*-TGA, the systemic and pulmonary circulations operate in parallel rather than in series. This anomaly results in recirculation of blood, deoxygenated blood in the systemic circulation, and oxygenated blood in the pulmonary circulation. Intercirculatory mixing is essential for survival. The typical presentation is that of cyanosis shortly after birth as the ductus closes in an otherwise healthy-appearing neonate. There is minimal or no response to the administration of oxygen. A restrictive foramen ovale can result in poor mixing and profound arterial hypoxemia, potentially progressing to metabolic acidosis and severe shock due to compromised tissue oxygenation. Less commonly, a high pulmonary vascular resistance accounts for severe cyanosis despite ductal patency and an adequate anatomic interatrial communication.

Congestive heart failure is unlikely even in the presence of a PDA, VSD, or CoA in the first few days of life. Concomitant shunts at the ventricular or ductal levels are limited by the relatively high pulmonary vascular resistance which constraints significant shunt volumes.

Management

Without intervention, this defect is almost uniformly fatal. Preoperative management is determined by the adequacy of mixing between the parallel circulations. PGE_1 therapy frequently is used to enhance intercirculatory mixing. The goal of maintaining ductal patency is to increase the pulmo-

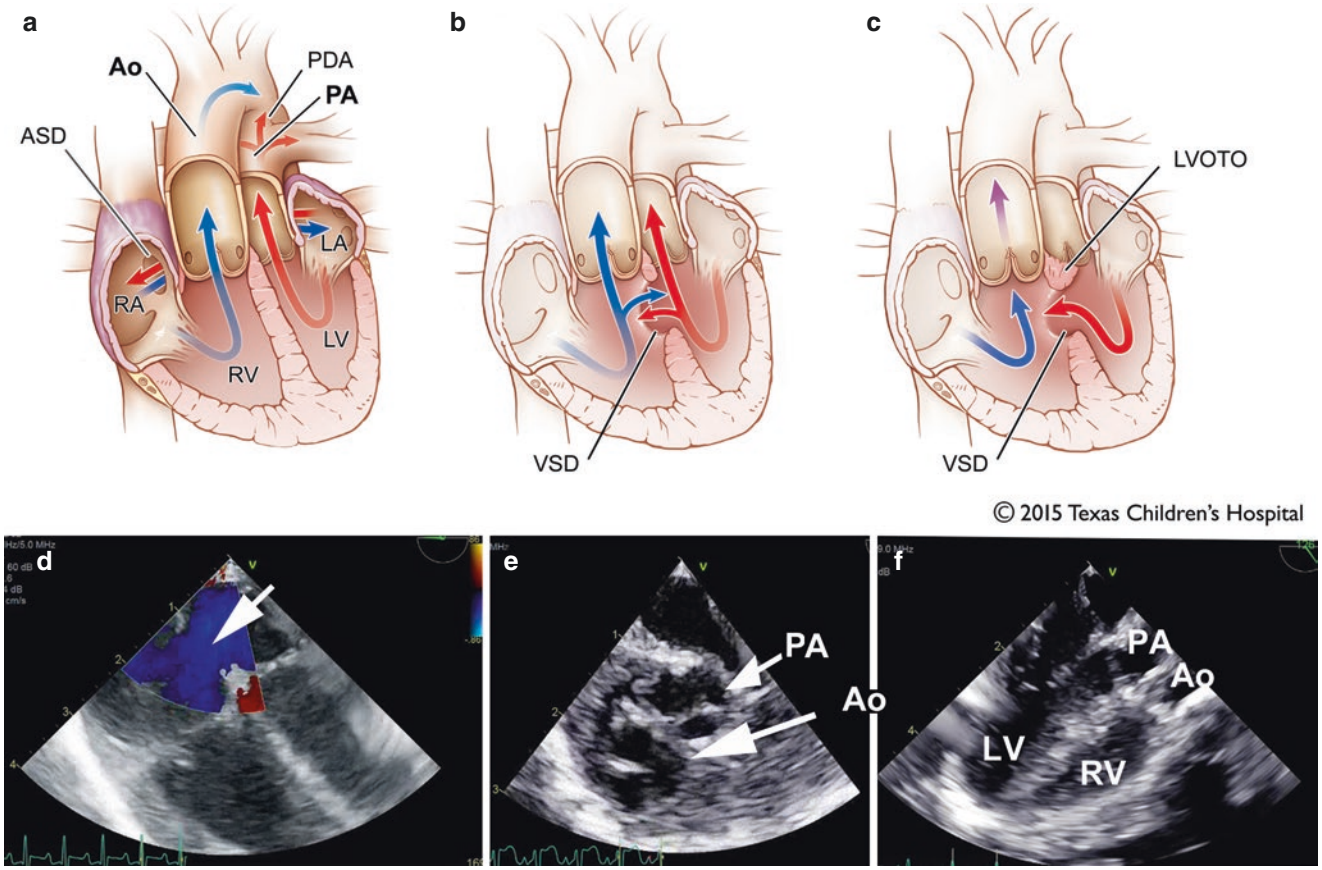

Fig. 11.5 **Panel a**, graphic representation of *d*-transposition of the great arteries (*d*-TGA) with intact ventricular septum. **Panel b**: *d*-TGA with ventricular septal defect (VSD) associated with shunting at the ventricular level. **Panel c**, *d*-TGA with left ventricular outflow tract obstruction (LVOTO). **Panels d–f**, preoperative transesophageal echocardiographic images displaying a large ASD with left-to-right shunting (white arrow) in a mid-esophageal four-chamber view (**panel d**); abnormal great artery relationship with an anterior and rightward aorta (Ao), and posterior and leftward pulmonary artery (PA) in a mid-esophageal short-axis view (**panel e**), and the abnormal ventriculo-arterial relations with a parallel course of the great arteries in a mid-esophageal long-axis view (**panel f**). Panels **a–c** reproduced with permission from Texas Children's Hospital. *LA* left atrium, *LV* left ventricle, *RA* right atrium, *RV* right ventricle

nary blood flow and the volume of pulmonary venous blood returning to the LA, which in turn increases the LA pressure to the extent that it stretches the interatrial communication, enhancing intercirculatory mixing. Balloon atrial septostomy is required to enlarge a restrictive foramen ovale if significant hypoxemia is present. Some centers favor an elective atrial septostomy in the neonate to allow for improved atrial mixing, discontinuance of PGE_1, and later surgery after feeding is established and the pulmonary vascular resistance decreases.

The arterial switch operation (Jatene procedure) is the operation of choice for uncomplicated *d*-transposition (Fig. 11.6). The intervention achieves anatomic correction and restores normal physiology. The surgical procedure involves transection of the great arteries above their semilunar valves, anastomotic connections to their appropriate respective outflows, translocation of the coronary arteries to the neoaortic root, closure of existing intracardiac communications, and repair of additional defects, as indicated. Early in the surgical experience, certain coronary patterns were considered to preclude this type of surgery, given the need to mobilize and reimplant these tiny vessels. Today, however, the concern is much less, and, in fact, many centers do not or rarely regard abnormal coronary patterns a contraindication for the arterial switch operation. Timing of the operation is important and it is undertaken before pulmonary vascular resistance decreases. This is to prevent deconditioning of the LV, given that it will become the systemic ventricular chamber upon completion of the operation. Hence, in most cases, the operation is performed within the first few weeks of life while the LV afterload [PVR] remains persistently increased due to the normally elevated pulmonary vascular resistance. Beyond the neonatal period, the approach to this lesion depends on numerous factors, but

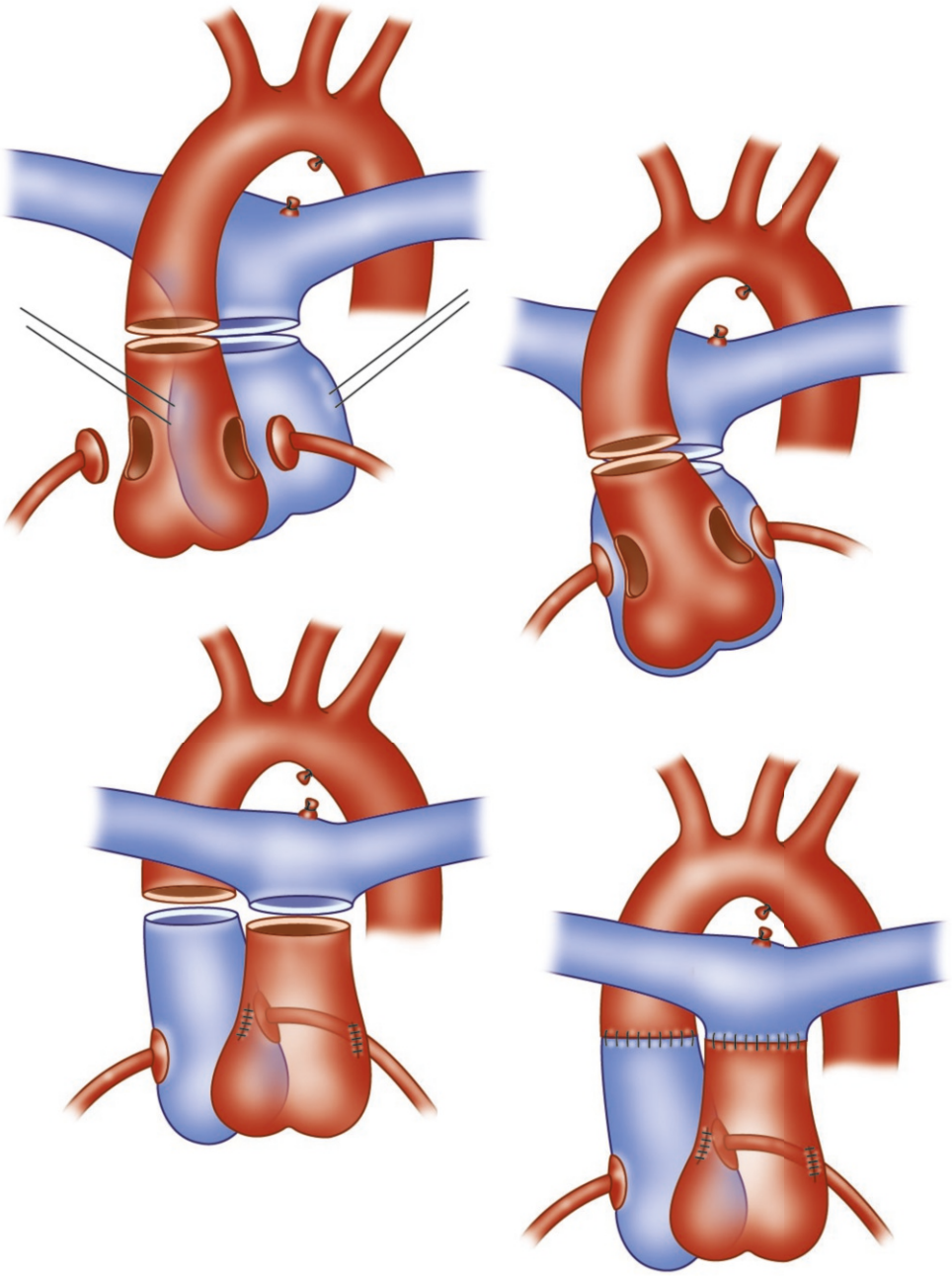

Fig. 11.6 Graphic representation of the arterial switch operation in *d*-transposition of the great arteries. *Upper left panel*, the ductus arteriosus/ligamentum is divided, and the great arteries are transected above the level of their native semilunar valves and roots. Coronary artery buttons are then removed from the usually anterior and rightward aorta. *Upper right panel*, the coronary arteries are translocated to the posterior "neoaortic" root (native pulmonary root). *Left lower panel*, the Lecompte maneuver is performed allowing for the main pulmonary artery to be mobilized in front of the neoaorta. *Right lower panel*, the aortic anastomosis is completed, and after repairing the defects in the native aorta ("neopulmonary artery") where the coronary buttons were removed, the pulmonary arterial anastomosis is completed

importantly on the ability of the LV to support the systemic circulation based on the presence or absence of associated defects and their impact on LV "preparedness."

Anesthetic Considerations

If a balloon atrial septostomy is required before corrective surgery, it can be undertaken at the bedside, in the intensive care unit, or in the cardiac catheterization laboratory. Frequently, the intervention is urgent due to profound arterial hypoxemia. The main goal is to maintain hemodynamic stability while an atrial communication is enlarged or created. Marked clinical improvement is seen with adequate atrial mixing. Access to emergency equipment, medications, and blood products is essential.

The use of intraoperative transesophageal echocardiography (TEE) is the standard at many congenital heart centers and may be used to confirm the anatomy (Fig. 11.5d–f) and the post-repair assessment.

Specific Issues

- *Myocardial ischemia*. Translocation of the coronary arteries involves manipulation, probing, and, in some cases, potential stretching or distortion of the vessels. These maneuvers in addition to other aspects of the repair can predispose the neonate to coronary artery spasm and/or myocardial ischemia. Thus, these patients require careful surveillance for compromise of myocardial blood flow (electrocardiographic monitoring of ST segments, LA pressure monitoring, regional wall motion assessment by TEE, examination of coronary Doppler blood flows). Inadequate coronary perfusion may cause ventricular dysfunction, failure of separation from CPB, or intractable ventricular arrhythmias. The post-bypass administration of a nitroglycerine infusion after surgery for *d*-TGA is routine in some centers.
- *Left ventricular compliance*. The LV in the neonate with *d*-transposition is relatively "stiff" and noncompliant immediately after surgery, which results in extreme sensitivity to the administration of excess volume, resulting in a significant increase in LA pressure and a decrease in cardiac output. Chamber overdistension is poorly tolerated, so fluids should be administered cautiously and guided by LA pressure, systemic arterial blood pressure, and qualitative echocardiographic assessment of LV size.
- *Pulmonary hypertension*. Because surgical correction is performed early in life before the normal decrease in pulmonary vascular resistance, pulmonary hypertension can be a problem in the immediate post-bypass period and postoperatively. If the case, strategies that support the RV, as well as the use of pulmonary vasodilators, should be considered.

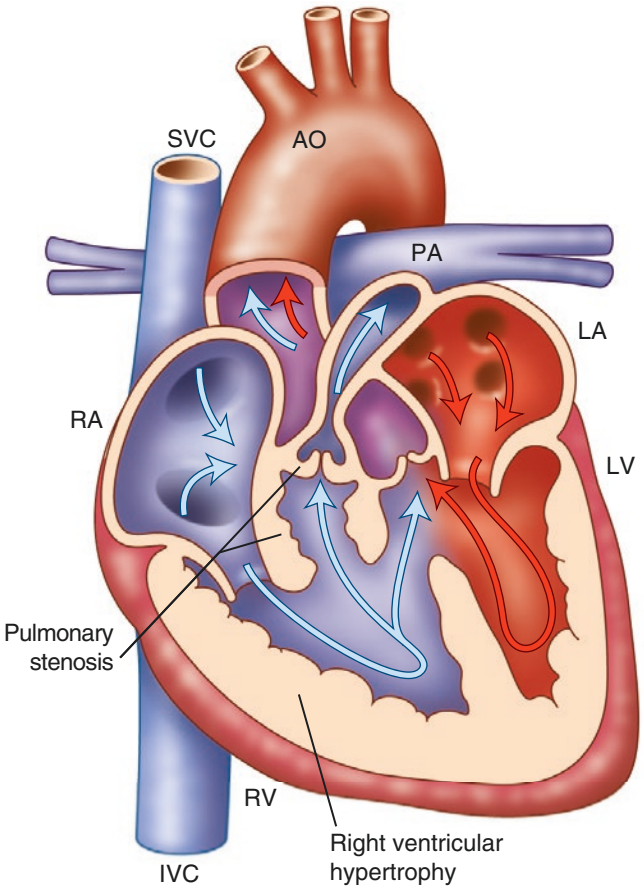

Fig. 11.7 Graphic representation of tetralogy of Fallot showing the classic features of this lesion: ventricular septal defect, pulmonary stenosis, overriding aorta (AO), and right ventricular hypertrophy. The potential various levels of right ventricular outflow tract obstruction are noted (subvalvar, valvar, and supravalvar). The right-to-left shunt across the ventricular septal defect (shown by the arrow) accounts for the presence of cyanosis in this defect. *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

Tetralogy of Fallot

Anatomic Features

Tetralogy of Fallot (TOF) is the most common cause of cyanotic heart disease in later childhood, accounting for approximately 6% to 11% of CHD. The absence of cyanosis or the failure to recognize mild cyanosis immediately after birth explains why TOF is often diagnosed beyond the neonatal period and is not recognized as the most common cyanotic heart defect in the neonate.

The four components of TOF in the classic lesion include a large VSD, right ventricular outflow tract (RVOT) obstruction, Ao override, and RV hypertrophy (Fig. 11.7) [62]. Anterior and cephalad displacement of the infundibular septum during cardiac development, also referred to as malignment of the outlet septum with respect to other portions of the ventricular septum, is considered the fundamental pathology responsible for the defects in this lesion [63]. The wide spectrum of clinical manifestations in tetralogy is due to the variable anatomic features, particularly the severity of the RVOT obstruction. Associated pathology includes an atrial communication, additional VSDs, a persistent connection from a left superior vena cava (LSVC) to the coronary sinus, coronary artery anomalies, and variants of Ao arch laterality or branching pattern. Concomitant lesions such as a complete atrioventricular septal defect can be present in some cases (colloquially referred to as "tet-canal" defect). Pulmonary atresia with a VSD is considered to represent an extreme form in the TOF spectrum.

Pathophysiology

The obstruction to RV outflow in TOF, which is often found at multiple levels, has variable dynamic and fixed compo-

nents. The dynamic obstruction occurs only in the muscular infundibular region. In contrast, the fixed components occur at the subvalvar, valvar, and supravalvar regions and/or the branch pulmonary arteries. Cyanosis is caused by decreased pulmonary blood flow and right-to-left shunting across the VSD, with lower pulmonary to systemic blood flow. The nonrestrictive nature of the VSD combined with the RVOT obstruction explains how the right and left ventricular pressures equalize in this lesion. Sudden increases in RVOT obstruction combined with right-to-left intracardiac shunting herald the hypercyanotic episodes or "tet spells." These can lead to significant morbidity or even death, but fortunately are very rare in the neonate.

TOF has a spectrum of clinical presentations [64]. At one end, the acyanotic neonate with TOF has a large VSD and minimal RVOT obstruction that shunt blood across the ventricular communication typically in the left-to-right direction. Some degree of heart failure from pulmonary over-circulation may be present subsequently as the pulmonary vascular tone decreases, accounting for the "pink" form of TOF. At the other end of the spectrum, the cyanotic neonate with severe PS/near pulmonary atresia depends on a PDA and is in need of an intervention to ensure a stable pulmonary blood flow after the ductus arteriosus closes. In the middle of this continuum is the "classic" form of TOF, characterized by moderate pulmonary outflow tract obstruction and mild to moderate cyanosis at rest (systemic oxygen saturation ~ 80% to 90%). This condition is the case in most neonates, in whom increasing cyanosis can occur with crying, agitation, or pain.

A particular variant of TOF with potential significant clinical implications in the neonatal period is that associated with absent pulmonary valve syndrome. This pathology is characterized by a dysplastic pulmonary valve, various degrees of valvar stenosis, and regurgitation, in addition to the usual findings in TOF. Massive dilation of the main and branched pulmonary arteries in this defect results in abnormalities of the tracheobronchial tree. These anomalies can result in severe respiratory compromise due to air trapping and are frequently associated with significant morbidity related to poor pulmonary mechanics.

Management

The favored surgical approach in the neonate or very young infant with TOF associated with severe RVOT obstruction and significant cyanosis varies among institutions. Some centers advocate initial palliation with a systemic-to-PA shunt, most frequently in the form of a modified Blalock-Taussig (mB-T) shunt (graft between a subclavian artery and PA). This is performed via a lateral thoracotomy or median sternotomy approach and is followed by corrective surgery later in infancy. Other centers prefer, even in very young infants, a single-stage definitive repair consisting of closure of the VSD, relief of the RVOT obstruction, and repair of associated defects.

A meta-analysis of the outcomes after complete physiologic repair of TOF in the neonatal and post-neonatal periods reported that mortality rate increased threefold and the hospital stay increased 47%, including an 18% greater duration of intensive care stay when the defect was repaired during the neonatal period compared with repair after the neonatal period [65]. A large study querying 2363 children with TOF using the Pediatric Health Information System database compared the outcomes of those who underwent either complete repair in the neonatal period or staged repair. They found that the cardiac complication rate in hospital was greater and the risk of mortality at 7 to 30 days and 2 years follow-up was greater during repair in the neonatal period compared with a staged repair [66]. Early morbidity and greater mortality rates with neonatal complete repair as compared with a staged approach continue to be reported [67, 68].

Many technical aspects of the surgical intervention in TOF are variable and depend on the surgeon/institution [69, 70]. The relief of the RVOT/pulmonary obstruction can be accomplished through transatrial and/or PA access and, in some cases, through a ventriculotomy. An incision across the pulmonary annulus and placement of a transannular patch is necessary in some cases, usually related to annular hypoplasia, which is more likely in younger infants. With regard to closure of the VSD, the approach can be a transatrial, transventricular, or combined, based on the surgeon's preference. Although a ventriculotomy or the need for a transannular patch can impact the long-term outcome, some prefer palliation rather than correction in very young infants. Alternative medical temporizing measures at some centers include the use of beta-adrenergic receptor antagonists to minimize the risk of infundibular "spasm" and associated hypercyanotic events. In selected cases, cardiac catheterization procedures such as percutaneous balloon pulmonary valvuloplasty or stenting of the ductus arteriosus or stenting of the RVOT can be beneficial while the infant awaits corrective surgery [71].

Anesthetic Considerations

During anesthetic care, the main concern in the unrepaired neonate with TOF is the potential for hypercyanotic episodes that can result in profound hypoxemia and significant morbidity [72]. These episodes can be triggered by crying, light anesthesia, pain, hypovolemia, sympathetic stimulation (or sympathomimetic drugs), or anesthetic-related decreases in systemic vascular tone with augmentation of the right-to-left shunting. Immediate management of an acute spell usually requires titration of a systemic vasoconstrictor drug (phenylephrine, norepinephrine, or vasopressin). Augmenting the

cardiac preload by administering fluids to facilitate forward flow across the obstructed RVOT can also help. Beta-blockers (e.g., esmolol or propranolol) can be given in an effort to decrease heart rate and enhance diastolic filling time, while also relaxing the dynamic RVOT, but should be used with great caution in the neonate. A measure that is usually considered once the neonate has been stabilized is blunting of the sympathetic tone by increasing the anesthetic depth by the administration of a sedative, opioid, or inhalational agent. Carefully titrated inhalational agents are especially advantageous in view of their cardiac depressant effects on the RVOT. Halothane was ideal for the child with TOF but is not readily available now. Sevoflurane has largely replaced halothane for induction. This agent does not increase the heart rate in doses <1.5 MAC and may be a better choice than isoflurane for maintenance [73]. Both agents cause the same amount of vasodilation. During cardiac surgery, a hypercyanotic episode is rarely refractory to treatment necessitating emergent initiation of CPB. The main goals of anesthetic care of the neonate with TOF are to minimize the potential for further increases in right-to-left shunting, promote forward pulmonary blood flow, and preserve myocardial function. Even issues that are known to minimally influence the physiology of other forms of CHD can impact that of the neonate with TOF. An example is the potentially detrimental effect of mechanical ventilation on intrathoracic pressure, further reducing pulmonary blood flow.

Specific Issues

- *Pulmonary vascular resistance*. In general, pulmonary vascular tone does not substantively affect the physiology of this lesion, although the normally increased pulmonary vascular resistance in the neonate can impede forward flow across the outflow tract. It can have important implications regarding perioperative management and surgical decision-making as it complicates the assessment of the severity of the RVOT obstruction. Therefore, a reasonable anesthetic goal is to minimize acute increases in pulmonary vascular tone.
- *Arterial blood pressure monitoring*. The presence of an aberrant subclavian artery, a relatively common associated finding, should be considered in the selection of sites for arterial line placement. In this setting, insertion and manipulation of a TEE probe for intraoperative imaging during complete repair can compress the retroesophageal vessel leading to blunting or disappearance of the blood pressure tracing. When palliation in the form of a mB-T shunt is anticipated, the arterial catheter must be placed in a site other than the one supplied by the vessel where the vascular graft is planned to allow for uninterrupted assessment of arterial blood pressure throughout the case.
- *Aortic arch sidedness*. During palliative surgery via thoracotomy, Ao arch sidedness can influence the site of shunt placement and, hence, the surgical approach (right versus left thoracotomy). Although Ao arch anatomy is determined preoperatively, it is a matter of consideration during surgical positioning.
- *Coronary artery anomalies*. These anomalies are present in 5% to 12% of patients with TOF and potentially impact the surgical procedure. The left coronary artery, for example, can originate anomalously from the right coronary artery and course across the RVOT and near or at the location of a planned transannular incision, requiring a modification in the usual surgical plan.
- *Effects of surgery*. It is important to highlight the impact of the surgical intervention on the physiology and influence on perioperative care as follows:
  - Transannular incision and patch augmentation during definitive surgical repair of TOF invariably lead to pulmonary regurgitation because the intervention violates the integrity of the annulus and valve. In some cases, the relatively "stiff" RV limits the regurgitant volume, and this restrictive physiology is well tolerated initially [74]. However, in other infants, the acute RV volume load exacerbates an underlying element of diastolic dysfunction. This issue, compounded by some degree of systolic impairment related to myocardial edema, ischemic time, mechanical effects of the manipulations of the heart, and injury to the anterior RV wall resulting from the ventriculotomy/transannular patch, can complicate the postoperative course. This may be further compounded by the presence of residual lesions (i.e., ventricular level shunting). The consequence is a low cardiac output state manifested in the first 24 h postoperatively. In patients with severe low cardiac output syndrome, spontaneous or negative pressure pulmonary ventilation can improve cardiac output and cerebral oxygenation [75, 76].
  - After complete repair, RV function can be impaired as previously described, and inotropic support may be required. However, it should be emphasized that inotropic agents can influence the postoperative assessment of the adequacy of the repair, because tachycardia and increased inotropy can exacerbate any residual RVOT gradient.
  - Pathology such as residual VSDs or RVOT obstruction, or significant tricuspid regurgitation may not be well tolerated in this particular patient group.
  - An intentional atrial communication, in the form of a patent foramen ovale or small atrial septal defect, might be created during corrective surgery to facilitate postoperative care in anticipation of decreased RV

compliance. This communication allows for maintenance of cardiac output at the expense of a small amount of atrial level right-to-left shunting and a mild degree of arterial hypoxemia.

- *Junctional ectopic tachycardia (JET).* JET consists of a narrow QRS tachycardia (heart rate greater than 170 beats per minute), atrioventricular dissociation, and a ventricular rate faster than the atrial rate [77]. The loss of the atrial contribution to ventricular filling and shortened diastolic filling time can have significant hemodynamic effects in this vulnerable patient. This arrhythmia can occur in the immediate postoperative period after surgery for CHD, including TOF repair [78, 79]. Strategies to manage this arrhythmia include sedation (to reduce sympathetic tone), decrease in the level of inotropic support, surface cooling (32–34 °C), correction of electrolyte disturbances, various forms of pacing, and administration of magnesium. Pharmacological treatment with intravenous agents (e.g., amiodarone, procainamide, sotalol) may be indicated in some cases [80, 81]. Over the last several years increasing clinical experience with dexmedetomidine suggests that an infusion of the drug after CPB decreases postoperative JET in pediatric patients [82, 83]. Pretreatment with a beta-blocker may also reduce the incidence of this arrhythmia [84]. Extracorporeal membrane oxygenation support (ECMO) and/or extracorporeal cardiopulmonary resuscitation (ECPR) should be considered in the management of hemodynamically unstable primary arrhythmias as an emergent lifesaving procedure [85, 86].
- *Restrictive physiology*. Some neonates post-tetralogy repair develop a syndrome referred to as "acute right ventricular restrictive physiology." This is characterized by a low cardiac output state, need for inotropic support, and prolonged intensive care stay. Using echocardiography, the physiology of RV restriction is manifested by Doppler evidence of antegrade pulmonary arterial flow in late diastole. The findings reflect transmission of atrial contraction into the MPA and the role of the RV as a passive conduit during this phase of the cardiac cycle [87, 88].

Total Anomalous Pulmonary Venous Return

Anatomic Features

Total anomalous pulmonary venous return (TAPVR) accounts for 2% of all CHD. It is characterized by drainage of all pulmonary venous blood back into the pulmonary circulation through remnants of vascular connections normally present during fetal life. The lesion represents an obligatory shunt as oxygenated blood from the pulmonary veins is diverted to the RA. This anomaly is classified into several types according to the main path by which blood in the anomalous pulmonary veins drains (Fig. 11.8): supracardiac, via a vertical vein to innominate vein or right SVC; cardiac, into the coronary sinus or RA; infracardiac, via a common pulmonary vein into the portal system, from there through the ductus venosus to the IVC; or mixed, a combination of the various types. In two-thirds of cases, this is an isolated lesion. In the remaining one-third of cases, TAPVD is associated with other defects (VSD, CoA, and complex CHD such as heterotaxy syndromes).

Pathophysiology

Anomalous pulmonary venous return is well tolerated in the fetus because of the limited pulmonary blood flow associated with the normally high pulmonary vascular resistance. In the first few days/weeks after birth, the presence or absence of obstruction along the pulmonary venous pathway plays a major role in the physiologic consequences of the defect. In the absence of pulmonary venous obstruction and high pulmonary blood flow, plus a nonrestrictive ASD, it is associated with a relatively high systemic arterial oxygen saturation (SaO_2) and adequate systemic cardiac output. Over time, however, RV volume overload and congestive symptoms of CHF ensue. This physiology of TAPVR can result in a late presentation. In contrast, a restrictive atrial communication leads to a greater degree of arterial hypoxemia and compromised systemic output. Pulmonary venous obstruction almost always is the norm in infradiaphragmatic TAPVR secondary to constriction of the ductus venosus. This latter condition is characterized by profound hypoxemia caused by decreased pulmonary blood flow and pulmonary venous congestion, pulmonary hypertension, and respiratory compromise. Relative "pseudo-hypoplasia" of left-sided cardiac structures can be seen in the affected neonate with TAPVR.

All forms of this lesion have complete mixing of systemic and pulmonary venous returns at the level of the RA. Right-to-left atrial shunting allows mixed blood to enter the LA, which is then ejected by the LV into the systemic circulation. The degree of hypoxemia depends on the severity of the pulmonary venous obstruction; it can be mild and mimic respiratory distress syndrome, or profound, in which case the infant will be moribund.

Management

Initial efforts are directed at stabilizing the neonate and establishing respiratory/hemodynamic support as necessary. Chest radiography can provide a clue as to the site of drainage and likelihood of obstruction (Fig. 11.9), and in most cases, a definitive diagnosis is established only by echocardiography. At times chest tomography may be done to further define the anatomy. Surgical intervention can be undertaken on an elective

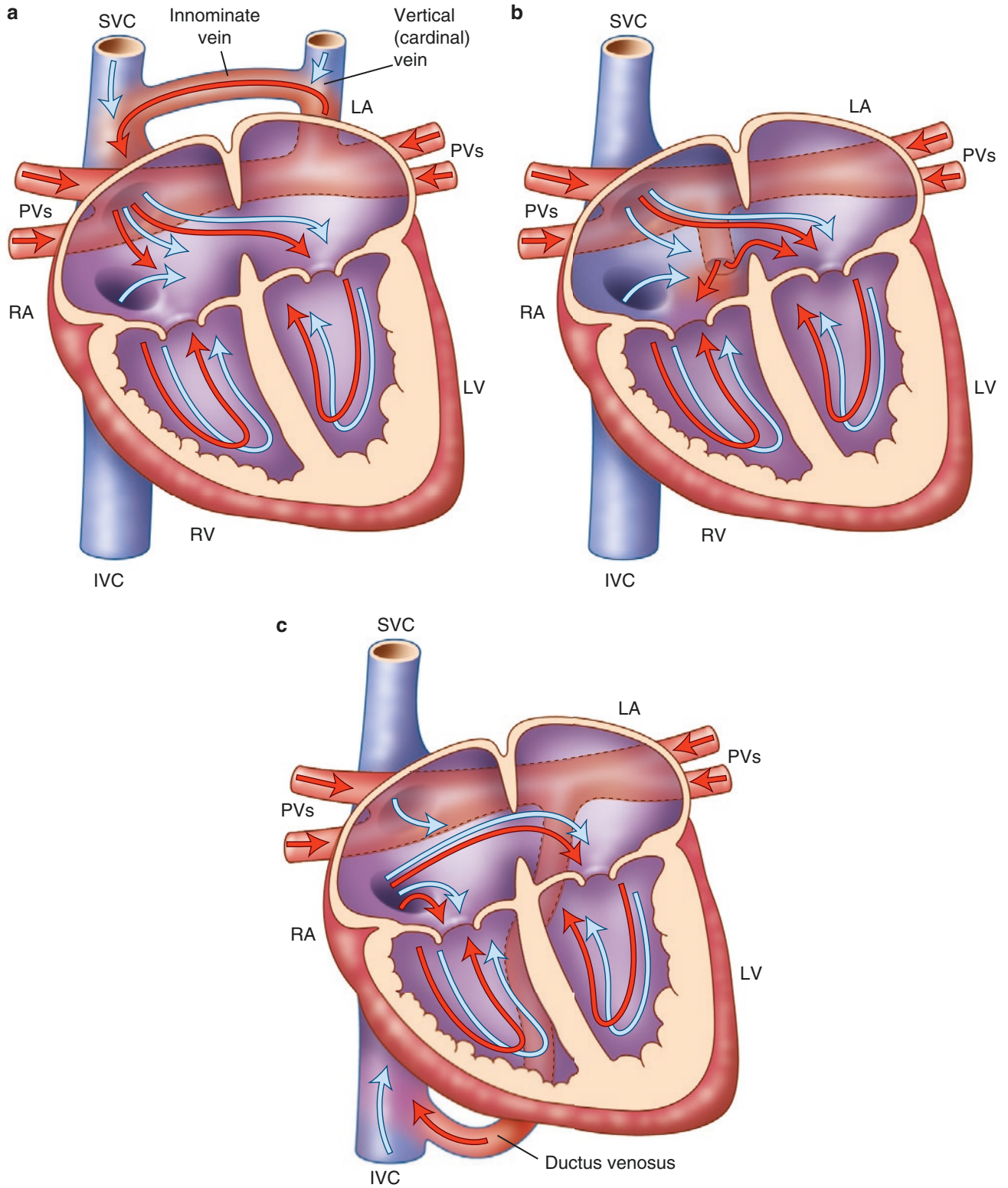

Fig. 11.8 Graphic representation of total anomalous pulmonary venous return. **Panel a**, supracardiac drainage. In this lesion the path of pulmonary venous drainage is from a vertical vein to the innominate vein into the right atrium (RA). In most defects an associated atrial septal defect is present. **Panel b**, cardiac drainage. In this pathology, the pulmonary veins (PVs) typically empty into the coronary sinus, draining into the RA. **Panel c**, infracardiac drainage. In this setting, PVs drain through the ductus venosus to the RA. Frequently this anomaly is associated with pulmonary venous obstruction. *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *SVC* superior vena cava

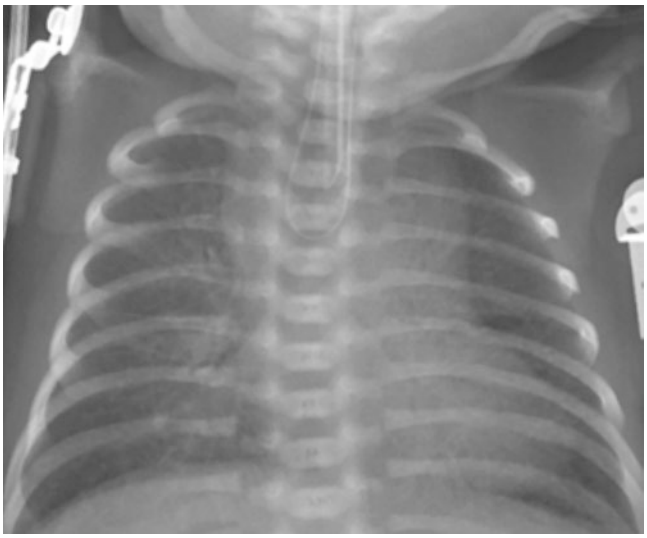

Fig. 11.9 Chest radiograph obtained in a neonate with obstructed supracardiac total anomalous pulmonary venous return showing the widened mediastinum due to the superior vena cava engorgement and pulmonary vascular congestion. A tracheal tube is present and an orogastric tube is noted to be coiled in the esophagus

basis if minimal or no pulmonary venous obstruction is present and the infant is doing well clinically. Most cases with obstruction require urgent or emergent surgery due to the presence of severe hypoxemia [89]. The administration of PGE_1 may be detrimental in the presence of severe obstruction as it further increases pulmonary blood flow, aggravating the obstruction and worsening oxygenation. However, in some cases PGE_1 may be beneficial as it influences vascular smooth muscle tone and may maintain the patency of the ductus venosus, thereby alleviating the obstruction. Regardless of the details of the anatomy in TAPVR, the surgical correction aims to reroute the drainage of the anomalous pulmonary veins into the LA.

Anesthetic Considerations

The main issues regarding the anesthetic care in these neonates before the pathology is addressed center around respiratory and hemodynamic support [90]. In the presence of pulmonary venous obstruction and severe hypoxemia, relatively high ventilatory settings that include the use of high peak inspiratory and positive end-expiratory pressures usually are required. The repair is frequently performed under deep hypothermic circulatory arrest (DHCA) or using low-flow perfusion. Upon separation from CPB, support of the RV with inotropic agents and pulmonary vasodilators is important in order to maintain cardiac output in the presence of an increase in pulmonary vascular resistance. This management aims at limiting the likelihood of a negative effect of the RV on the LV (ventricular interactions). The LV in this lesion is relatively noncompliant and is subject to failure. Blood volume overload can reduce stroke volume. Thus, fluid should be administered cautiously to prevent LV overdistension. This can be guided by using LA pressure monitoring.

Specific Issues

- *Pulmonary vascular reactivity*. There is a propensity in these infants to develop acute pulmonary hypertensive crises in the post-bypass or postoperative period due to a reactive pulmonary vascular bed. These episodes are prevented/managed by deep sedation and measures to decrease pulmonary vascular tone. The administration of pulmonary vasodilators, including inhaled nitric oxide, is indicated as required. In cases at risk, PA pressure monitoring via a surgically placed direct transthoracic catheter can facilitate management.
- *Echocardiography*. Placement and/or manipulation of a transesophageal probe can compress the pulmonary venous confluence and compromise hemodynamics. Epicardial echocardiography might be considered preferable for intraoperative imaging to assess the surgical results.
- *Partial anomalous pulmonary venous drainage*. Anomalous drainage of only one or two pulmonary veins is not uncommon in association with other forms of CHD. Usually this is of little physiological consequence in the neonatal period.
- *Postoperative pulmonary venous obstruction*. Approximately 15% of infants develop postoperative pulmonary venous obstruction, typically within 6 months of surgery [90]. This may be related to anastomotic stricture or to progressive intimal hyperplasia. The individual pulmonary veins can also develop stenosis. Interventions for management range from balloon angioplasty to reoperation.

Truncus Arteriosus

Anatomic Features

Truncus arteriosus (TA) is a relatively uncommon malformation, representing only 1% to 2% of congenital cardiac defects. Approximately one-third of infants with this anomaly have deletions of chromosome 22 (e.g., DiGeorge syndrome). In TA, also referred to as persistent truncus arteriosus or common arterial trunk, a single arterial root emerges from the heart, giving rise to the Asc Ao, PA, and coronary arteries (Fig. 11.10). An unrestrictive outlet VSD is almost always present and the origin of the common arterial trunk characteristically straddles the ventricular communication. This defect is thought to be caused by failure of the normal process of conotruncal septation that results in two great arteries.

There are several classifications proposed for TA [91–93]. In the most commonly used classification scheme described by Collett and Edwards, TA is subdivided into several subtypes (types I, II, III) based on the anatomical origin of the

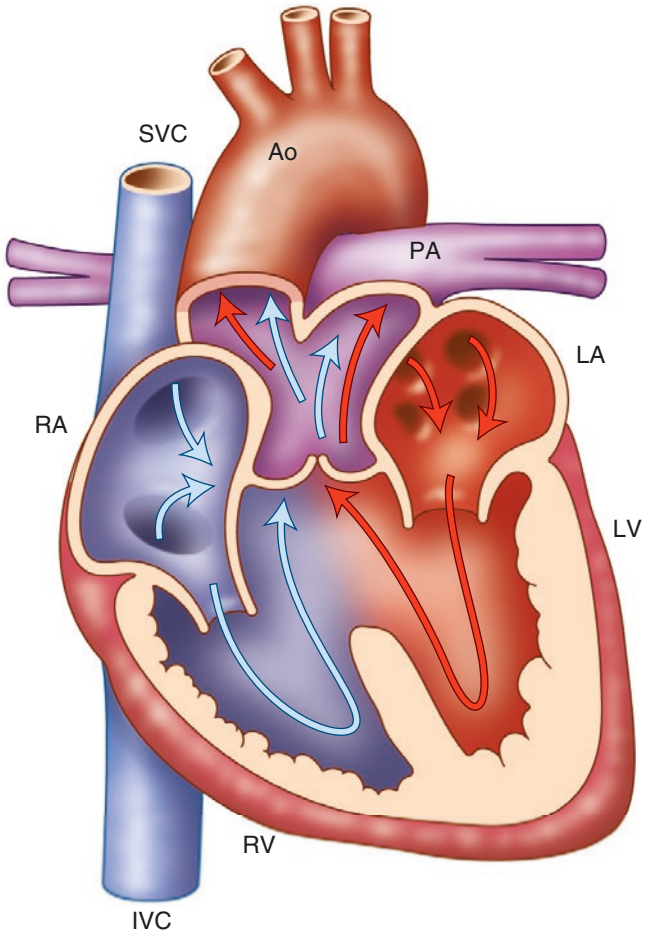

Fig. 11.10 Graphic representation of truncus arteriosus demonstrating the common truncal root with a biventricular origin. In this lesion, there is obligatory mixing of the systemic and pulmonary venous returns. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

pulmonary arteries from the arterial trunk [91]. The most common variant is one somewhere between types I and II, colloquially referred to as TA type 1½. Associated lesions include truncal valve issues (abnormal number of cusps, dysplasia, stenosis, regurgitation), abnormal origin and course of the coronary arteries, and Ao arch anomalies (right Ao arch and Ao arch interruption). The details of the anatomy can be defined by echocardiography in nearly all cases (Fig. 11.11).

Pathophysiology

Hypoxemia in TA is due to complete admixture of systemic and pulmonary venous blood as it emerges from both ventricles into the single arterial vessel. The hemodynamic repercussions of the defect relate to the direct physical communication between the systemic and pulmonary circulations at the level of the truncal root. This arrangement imposes a pressure and volume load to both ventricles further exacerbated by truncal valve pathology (stenosis or regurgitation), if present. The clinical features depend primarily on two factors: the pulmonary vascular resistance and the presence of any intrinsic stenosis in the pulmonary arteries. These variables determine the volume of blood that enters the pulmonary vascular bed from the truncal root.

The neonate usually is well compensated immediately after birth due to the normal relatively high pulmonary vascular resistance. As this decreases however, symptoms related to pulmonary over-circulation and congestive heart failure emerge. In the presence of branched PA stenosis, the neonate can remain clinically stable to the degree that pulmonary blood flow is adequately restricted. If the obstruction is severe, cyanosis can be significant.

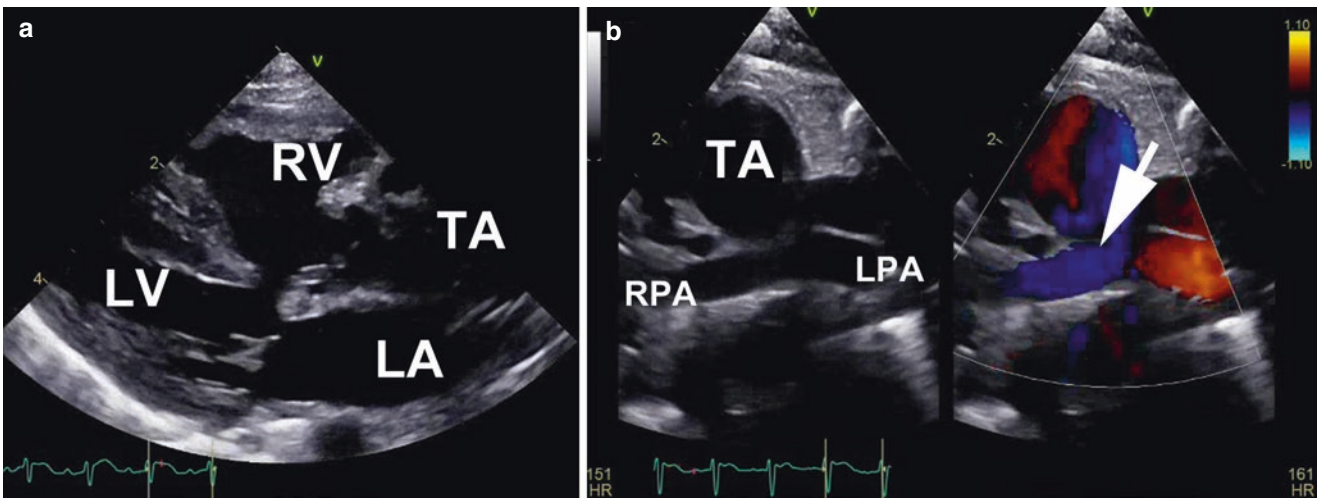

Fig. 11.11 Transthoracic echocardiographic images in a neonate with truncus arteriosus displaying the biventricular origin of the single arterial root in a parasternal long-axis view (**panel a**). This is a type II truncus arteriosus with normal caliber pulmonary arteries, arising separately from the left posterior aspect of the common trunk as shown by two-dimensional and corresponding color Doppler (**panel b**). White arrow shows the flow from the truncal root into the right pulmonary artery (RPA). *LA* left atrium, *LV* left ventricle, *RV* right ventricle, *TA* truncal artery, *LPA* left pulmonary artery

Management

Therapy for CHF is indicated preoperatively in most cases including inotropic support. The preferred management approach is surgical repair during the neonatal period. This consists of removing the PA(s) from the truncal root, repairing the ensuing defect, patching the VSD closed, reconstructing the RVOT, and repairing any associated pathology that may include the truncal valve. Early correction is indicated since pulmonary vascular obstructive disease can rapidly develop. There is a high incidence of a need for reintervention, which occurs frequently and has been attributed to problems with the RV to PA conduit and truncal valve [94].

Anesthetic Considerations

A major challenge in the perioperative care of the neonate with TA pertains to balancing the pulmonary and systemic vascular resistances to achieve cardiovascular stability during the pre-bypass period. A low pulmonary vascular resistance facilitates over-circulation that is associated with a steal phenomenon characterized by high systemic SaO_2, low diastolic arterial pressures, and a wide pulse pressure. This steal leads to impaired systemic output, hypotension, and compromised tissue oxygen transport. There is hypoperfusion of distal tissues, and the potential for myocardial ischemia. Thus, the likelihood for morbidity and critical events is high. TA is considered one of the congenital lesions most associated with a very high risk of adverse perioperative events [95].

The anesthetic management of the neonate with unrepaired TA therefore focuses largely on controlling pulmonary blood flow and maintaining adequate systemic output [94]. Reducing the inspired oxygen concentration where possible, to room air levels, and increasing arterial carbon dioxide tension ($PaCO_2$) to mild hypercarbic values are the most common strategies used to limit pulmonary blood flow by avoiding decreases in pulmonary vascular tone. Effects of the anesthetics, positive pressure ventilation, and changes in intravascular volume may pose challenges to managing pulmonary over-circulation during the pre-bypass period and systemic hypotension may occur (arterial blood pressure can decrease). Electrocardiographic changes suggestive of myocardial ischemia can be present. Agents that depress the myocardium or cause significant systemic vasodilation should be administered cautiously. In addition to limiting pulmonary blood flow, other strategies may be required to address systemic hypotension including fluid volume expansion, increasing the hematocrit, and infusing inotropes and vasoconstrictors for ventricular support as required. During cardiac surgery, a temporary snare can be placed around the MPA segment or one of the PA branches to mechanically restrict pulmonary blood flow and augment systemic output. As would be expected, this intervention is often followed by systemic arterial desaturation, necessitating an increase in the inspired oxygen concentration.

Specific Issues

- *Atrial level shunting*. In some cases, a small interatrial communication is left patent or is created intentionally to facilitate the postoperative course. In this setting, some degree of arterial desaturation is expected as a tradeoff benefit to the maintenance of cardiac output, particularly at times when right-sided/pulmonary artery pressures increase.
- *Residual lesions*. After surgery, volume loading on the LV, as imposed by a residual VSD or truncal valve regurgitation, may be poorly tolerated. The post-repair TEE examination is invaluable in: (1) excluding hemodynamically significant truncal valve stenosis, regurgitation, and RVOT obstruction, (2) interrogating for atrioventricular valve regurgitation and, (3) evaluating ventricular function.
- *Pulmonary hypertension*. Affected neonates are particularly vulnerable to developing acute increases in PA pressures during the post-bypass period and in the intensive care unit. This vulnerability can lead to acute decompensation, significant morbidity, and even death. The surgical placement of a PA pressure-monitoring catheter for perioperative management may be useful and is a matter of institutional preference. The perioperative management of pulmonary hypertensive crises is addressed in subsequent sections of this chapter.

Critical Aortic Stenosis

Anatomic Features

Congenital AS is present in 3% to 6% of all patients with CHD; however, symptomatic disease in the neonate or infant accounts for fewer than 10% of cases of Ao valve stenosis, consistent with the rare nature of the lesion. The valve in critical AS is characterized by leaflet fusion, frequently exhibiting a unicuspid appearance, or might be severely thickened and dysplastic (Fig. 11.12). The Ao annulus, root, and Asc Ao typically display some element of hypoplasia. In many cases, LV dilation in combination with poor systolic function and mitral regurgitation is present. This condition is frequently associated with infarction and atrophy of papillary muscles as well as endocardial fibroelastosis (EFE). Various degrees of LV hypoplasia and mitral and Ao arch hypoplasia also can be present in some infants.

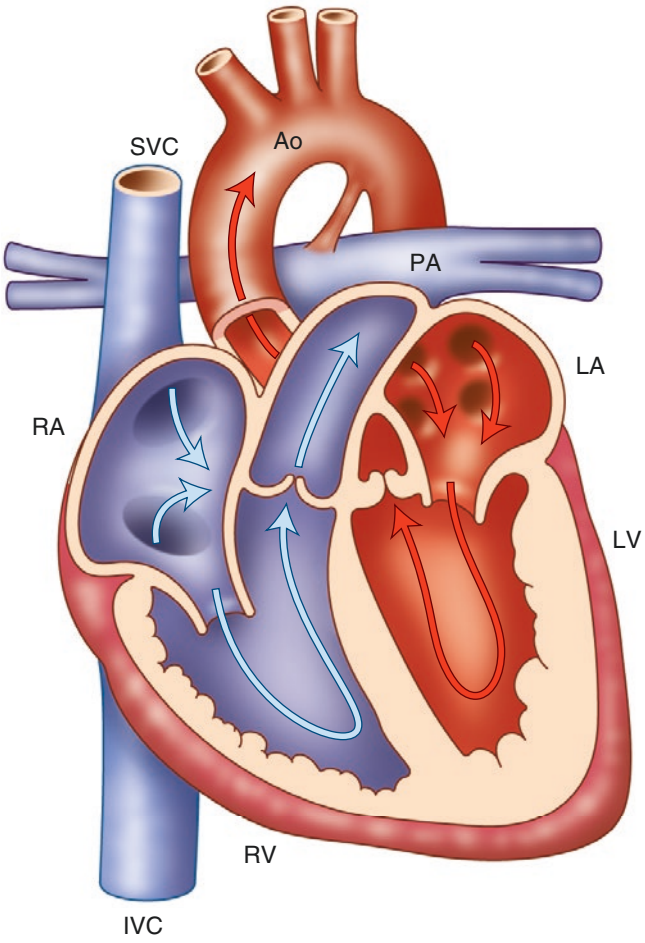

Fig. 11.12 Graphic representation of critical aortic stenosis. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

Pathophysiology

Obstruction to LV outflow due to a restricted Ao valvar orifice leads to increased LV systolic pressure, a transvalvular pressure gradient, increased myocardial force, and LV wall stress. The hypertrophied myocardium is at risk for developing subendocardial ischemia as a consequence of an imbalance in the ratio of myocardial oxygen supply and demand. Left ventricular EFE results from compromised subendocardial oxygen delivery secondary to myocardial ischemia. Fibrotic myocardial changes lead to severely impaired ventricular function, resulting in marked increases in LV end-diastolic and LA pressures. The presence of EFE along with LV dilation and/or dysfunction carries a poor prognosis. A large gradient across the Ao valve places a severe stress on the function of the LV. When considering the degree of the aortic valve stenosis, it should be recognized that a poorly functioning LV may not be able to generate a significant pressure gradient even in the presence of severe obstruction. The transvalvular pressure gradient must be considered within the context of the systolic function of a ventricle.

Critical AS in the fetus can lead to hydrops caused by ongoing subendocardial ischemia and severe myocardial dysfunction. In most cases of critical disease in the neonate, antegrade flow through the Ao is inadequate to maintain cardiac output, and right-to-left shunting through the ductus arteriosus accounts for most of the systemic blood flow. In fact, retrograde flow through the aortic arch via the ductus may in some cases be responsible for coronary and cerebral perfusion.

The neonate presents with signs of severe heart failure or frank shock, often temporally related to constriction or closure of the ductus arteriosus. Clinical evidence of congestive heart failure in the neonate includes tachypnea, poor feeding, diaphoresis with feeds, failure to thrive, hepatomegaly, and a gallop rhythm. A low cardiac output state, associated with severe ventricular dilation and dysfunction, is manifested by poor peripheral perfusion, pallor, cool extremities, and lactic acidemia. Papillary muscle infarction, usually associated with severe mitral regurgitation, can be part of a grim presentation. Systemic compensatory responses consist of tachycardia, systemic vasoconstriction, and increased blood volume. The physiologic alterations are complex and impact not only the cardiovascular system but also other major organs.

Management

Fetal congestive heart failure and hydrops present a unique challenge. Transplacental digitalization has been used to treat fetal heart failure. Critical AS without intervention carries a high mortality rate in the neonate. In recent years, fetal interventions for critical AS have been performed at specialized heart centers in an effort to alter the natural history of the condition in utero, potentially obviating progression of the disease [96, 97]. An analysis of the outcomes after in utero aortic ballooning in a series of infants with AS at Boston Children's Hospital estimated the survival to be 80 ± 4% at 1 year and 75 ± 5% at 5 years after ballooning. Outcomes were better in biventricular children with freedom from cardiac death of 96 ± 4% at 5 years and 84 ± 12% at 10 years, respectively [98]. Long-term outcome studies are needed to determine the impact of fetal aortic valve interventions on the disease process. Prenatal maternal oxygen therapy has also been attempted as a means to increase fetal pulmonary venous return, promoting filling to left heart structures and changes in LV geometry and promoting antegrade aortic flow [99, 100]. Therapy with PGE_1 maintains systemic perfusion and is life-saving. Concomitant therapy in the critically ill neonate

usually consists of mechanical ventilatory support to reduce the work of breathing, diuretic therapy, and infusion of inotropic agents to augment systemic output as needed. In some cases, afterload reduction is used cautiously.

Treatments for the primary pathology in aortic stenosis include percutaneous balloon aortic valvuloplasty and surgery. Transcatheter balloon valvuloplasty can be performed as a palliative procedure to relieve obstruction, permit recovery of LV function, and allow the patient to grow before surgery. These catheter interventions may be favored in some institutions. The choice of surgical intervention is influenced by factors such as size of the Ao annulus, aortic root, subaortic area, adequacy of the mitral valve and LV dimensions, and coexisting defects. Surgical and medical approaches include aortic valvotomy (open/closed), commissurotomy, aortic homograft placement, Ross procedure, Ross-Konno operation or other root-enlargement procedures, Damus-Kaye operation, and Norwood palliation. In some infants, cardiac transplantation may be the only feasible option at any time during their clinical course. Mechanical circulatory support may be considered at several points during the care as a bridge to an intervention, for postcardiotomy failure, or while awaiting cardiac transplantation.

Anesthetic Considerations

The care of the neonate with critical AS can be extremely challenging. Important anesthesia management decisions include carefully considering the potential myocardial depressant effects of drugs, anesthetic agents, and other perioperative interventions. Hemodynamic decompensation can occur during induction of anesthesia or at any time during a catheter or surgical intervention. Even the most careful anesthesia induction can result in cardiovascular instability and cardiac arrest as sedatives/anesthetic agents decrease sympathetic tone, which may be the primary compensatory mechanism. Cardiac massage may be ineffective because of the restrictive Ao valve orifice; therefore, one should recognize the potential for untoward events and proceed extremely cautiously. Having immediate access to emergency drugs and a defibrillator is vital. In addition advanced discussions regarding the potential need for urgent circulatory support during either the catheter-based intervention or the pre-bypass period should be documented. It is prudent for the surgery and perfusion teams to be immediately available during induction of anesthesia and throughout the procedure, whether catheter- or surgical-based.

It is important to continuously optimize ventricular filling and function without overlooking the potential detrimental effects of volume overload in the failing heart. Consider also the increased myocardial work and decreased ventricular filling times associated with the use of inotropic drugs.

Specific Issues

- *Transcatheter interventions*. Complication rates for transcatheter procedures in the neonate are greater than in older infants and children. Potential problems include bleeding, arrhythmias, transient myocardial ischemia during balloon inflation, development of or increase in the severity of aortic regurgitation, and vascular compromise related to access. Other complications such as cardiac perforation and tamponade should also be considered and prepared for accordingly.
- *Post-bypass problems*. In the post-bypass period, major issues include residual systemic outflow obstruction, aortic regurgitation resulting from or exacerbated by the intervention, hemodynamic perturbations due to associated defects, and myocardial dysfunction (preexisting and post-CPB).

Hypoplastic Left Heart Syndrome

Anatomic Features

Hypoplastic left heart syndrome (HLHS) accounts for approximately 2% of CHD, but 23% of neonatal deaths [101]. The morphologic features of this malformation include aortic atresia or stenosis, mitral atresia or stenosis, Asc Ao and arch hypoplasia, CoA, PDA, and an atrial level communication (Fig. 11.13) [102]. The pathology represents one of the most common forms of univentricular congenital malformation. Although HLHS is considered a spectrum of disease and the degree of LV hypoplasia and systemic outflow obstruction varies, the LV in the classic lesion (aortic and mitral atresias) is significantly underdeveloped and the Asc Ao is markedly hypoplastic [103].

Pathophysiology

HLHS is usually diagnosed either in utero by fetal echocardiography or immediately or very soon after birth. Most affected neonates are born at term and appear normal at birth. Because right-to-left shunting across the ductus arteriosus provides for the entire systemic blood flow in the case of aortic atresia, it is considered a “ductal-dependent circulation”. The atrial communication allows for the egress of pulmonary venous return into the RA, where it mixes with the systemic venous blood entering the RV and MPA.

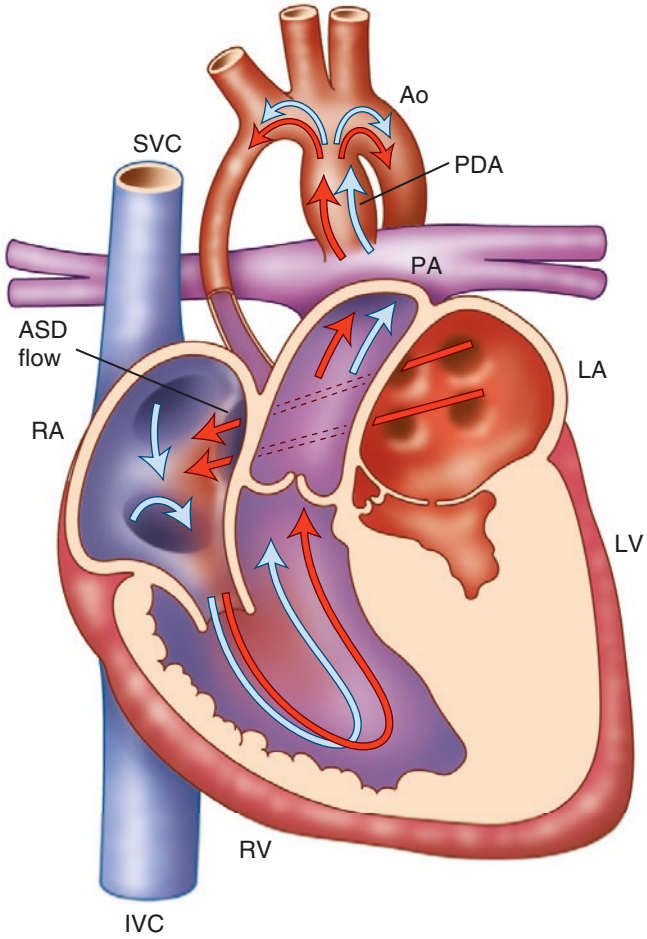

Fig. 11.13 Graphic representation of hypoplastic left heart syndrome. Note the small left-sided cardiac structures and direction of flow across the patent ductus arteriosus (PDA) (right-to-left shunting). The ductus allows for antegrade blood flow into the descending aorta (Ao) and retrograde flow around the aortic arch. An atrial communication allows for unobstructed egress of left atrial blood. *ASD* atrial septal defect, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

The clinical presentation in HLHS varies; some infants display cyanosis and/or features of pulmonary vascular congestion and others present with ominous signs of low cardiac output and impending or frank cardiovascular collapse. Acute decompensation is associated with ductal constriction and hypoperfusion of systemic vascular beds, resulting in metabolic acidosis, lactic acidemia, and in some cases, a shock-like picture. The shunted blood across the ductus arteriosus not only serves as the entire source of systemic cardiac output but also provides coronary blood flow because there is absent (aortic atresia) or virtually no antegrade flow through the Ao valve (critical AS). An aspect of the pathology that influences the clinical presentation is the degree of restriction across the interatrial communication or sometimes the presence of an intact atrial septum. On occasion, a decompressing vein allows for passage of LA blood elsewhere into the circulation. If this is not the case, the critically ill neonate displays profound hypoxemia and acidosis requiring immediate attention. This condition represents a major clinical problem and potentially a poor outcome.

Management

The initial management of the neonate with HLHS should aim to optimize the clinical status of the neonate and maintain ductal patency with an infusion of PGE_1. Mechanical ventilation, correction of acid-base status, and inotropic support may be necessary. The mainstay of management is to adjust the ratio of pulmonary to systemic blood flow (Qp/Qs) and to optimize oxygen delivery (Fig. 11.14) [104]. The neonate with a high PaO_2 caused by pulmonary over-circulation may have inadequate systemic blood flow. This condition will be associated with metabolic acidosis and result in problems related to decreased perfusion of metabolically active organs (e.g., necrotizing enterocolitis due to impaired splanchnic blood flow).

Measures must be implemented to maintain a relatively high pulmonary vascular resistance, in order to limit the pulmonary blood flow and to increase the systemic blood flow. In most cases, maintaining normocarbia or mild hypercarbia, and/or limiting the fraction of inspired oxygen concentration, will achieve this goal. The administration of added nitrogen to deliver a hypoxic gas mixture also has been used. Carbon dioxide may be added to inspired gases to increase pulmonary vascular tone and favor the balance of the Qp/Qs [105, 106]. In a study that assessed the effects of inspired gas mixtures to reduce pulmonary over-circulation and improve systemic perfusion, 3% inspired carbon dioxide improved cerebral oxygenation and mean arterial pressure, whereas a hypoxic mixture (17% inspired oxygen) affected neither [107].

Various approaches have been utilized to manage neonates and infants with HLHS reflecting the ongoing challenges in their care [101, 108–112]. Options include comfort care and no intervention, in which case death is almost assured, a stepwise palliative surgical strategy; an initial combined catheter-surgical approach (hybrid procedure) and subsequent step palliation; or cardiac transplantation [113, 114].

The initial surgical strategy for HLHS during the neonatal period is referred to as Stage I palliation or the Norwood procedure. It involves (1) neoaortic reconstruction using the native pulmonary root and homograft material to relieve the systemic outflow tract obstruction, (2) an atrial septectomy to allow for unobstructed drainage of the pulmonary venous return into the RA, and (3) creation of a reliable source of pulmonary blood flow through either a mB-T shunt (Fig. 11.15) or an RV to PA conduit (Sano modification, Fig. 11.16; Brawn modification, Fig. 11.17) [115]. The RV

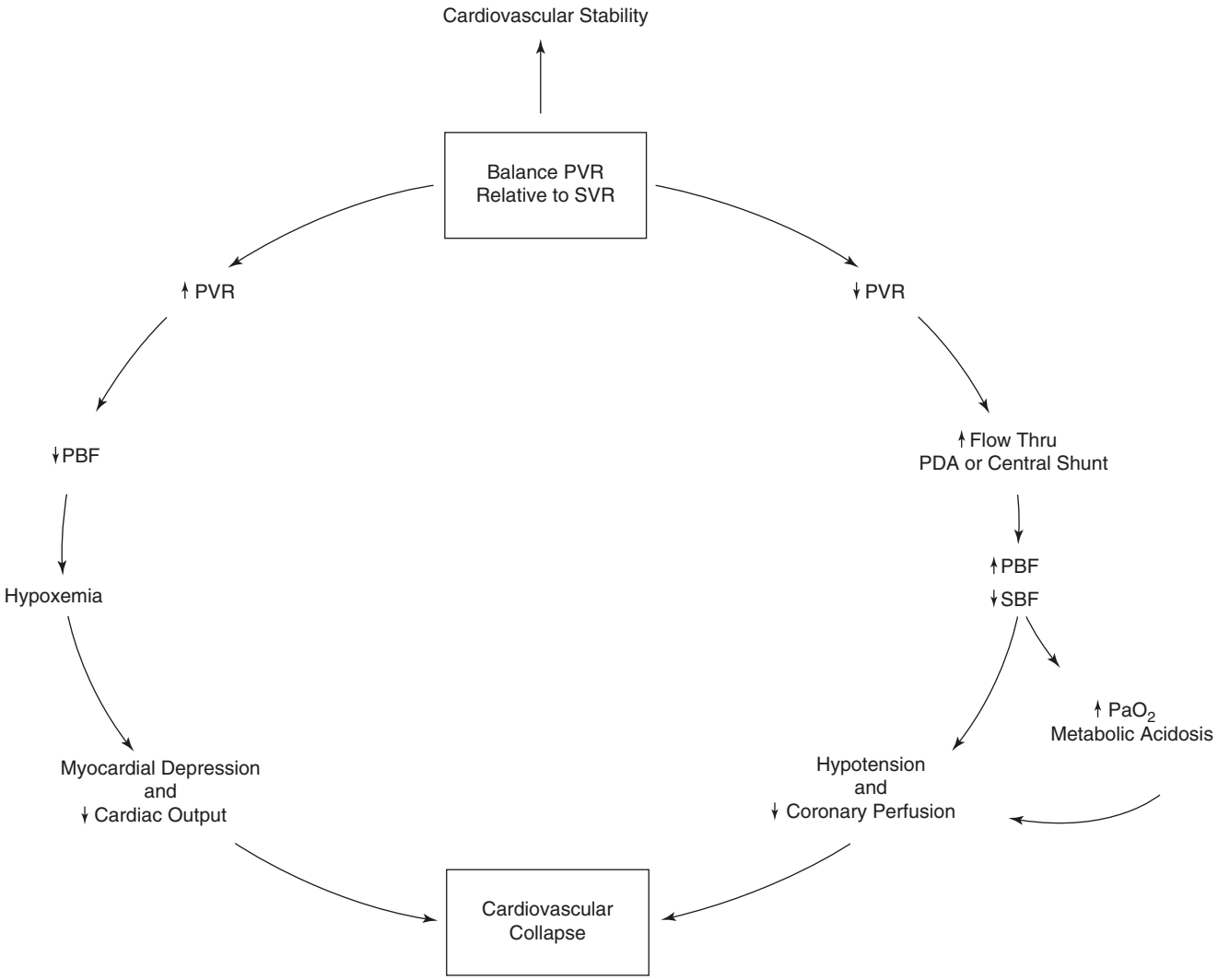

Fig. 11.14 Physiologic balance between the systemic and pulmonary circulations required for hemodynamic stability in the infant with hypoplastic left heart syndrome prior to and following palliation. Reproduced with permission from Hansen DD, Hickey PR. Anesthesia for hypoplastic left heart syndrome: use of high-dose fentanyl in 30 neonates. *Anesth Analg* 1986;65:127–132. *PBF* pulmonary blood flow, *PDA* patent ductus arteriosus, *PVR* pulmonary vascular resistance, *SBF* systemic blood flow, *SVR* systemic vascular resistance

thus becomes the chamber that supports both circulations. This operation is associated with potential significant perioperative morbidity and mortality [116]. In fact, the Norwood operation represents one of the greatest risk interventions in congenital heart surgery.

The hybrid procedure for HLHS represents an alternate palliative option to Stage I reconstruction during the neonatal period (Fig. 11.18) [117, 118]. This approach involves a combined catheter-based and surgical strategy wherein a stent is deployed by the interventional cardiologist across the ductus arteriosus to maintain patency and bilateral bands are placed across the PA branches by the surgeon to restrict pulmonary blood flow. The interatrial communication is enlarged (via balloon atrial septostomy) usually during or within a few days after this procedure to diminish the gradient across the interatrial septum. The hybrid approach delays Ao reconstruction until later in infancy and is considered of potential benefit, as the fragile neonate is not subject to CPB or associated techniques such as DHCA. Although it remains unclear which patients derive the most benefit from this strategy, neonates with low birth weight may have increased survival when this approach is used instead of the Norwood operation [119, 120]. In these infants, the subsequent Norwood reconstruction is combined with the creation of a superior cavopulmonary connection or Glenn anastomosis (Stage II palliation), thus effectively merging the first two

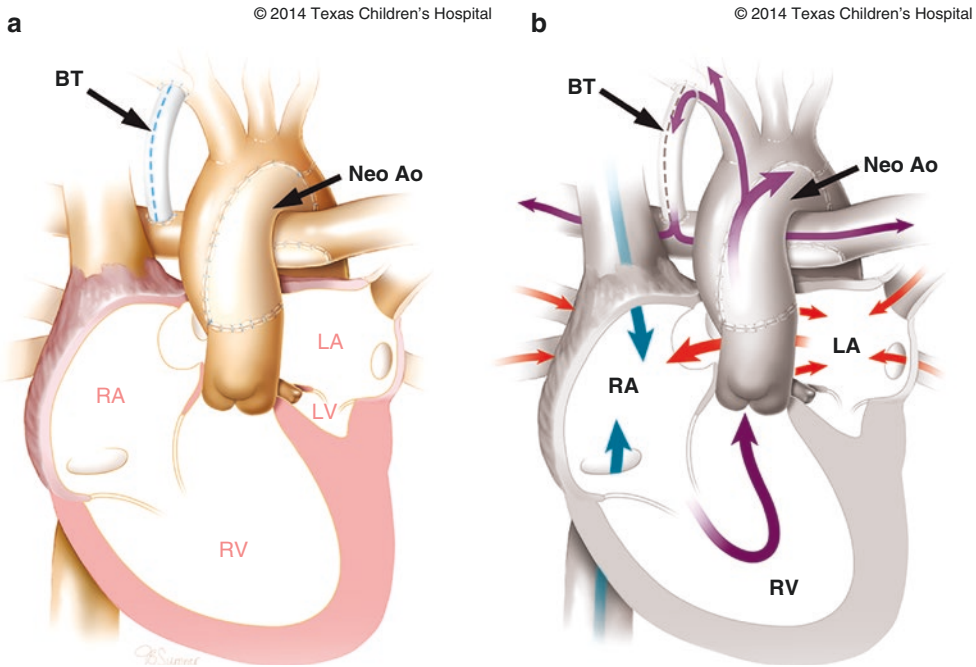

Fig. 11.15 **Panel a**, graphic representation of the Norwood procedure with modified Blalock-Taussig shunt (BT). **Panel b**, similar graphic showing the direction of blood flow after palliation with shunting at the atrial level and pulmonary blood flow provided by the shunt. Reproduced with permission from Texas Children's Hospital. *Neo Ao* neoaorta, *RA* right atrium, *RV* right ventricle, *LA* left atrium, *LV* left ventricle

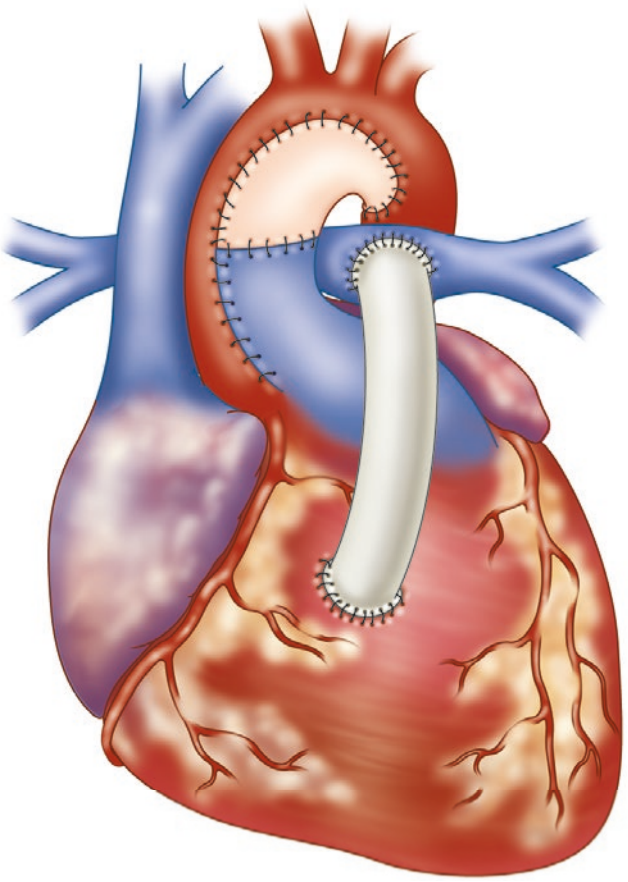

Fig. 11.16 Graphic representation of the Sano modification of the Norwood procedure with a right ventricular to pulmonary artery conduit

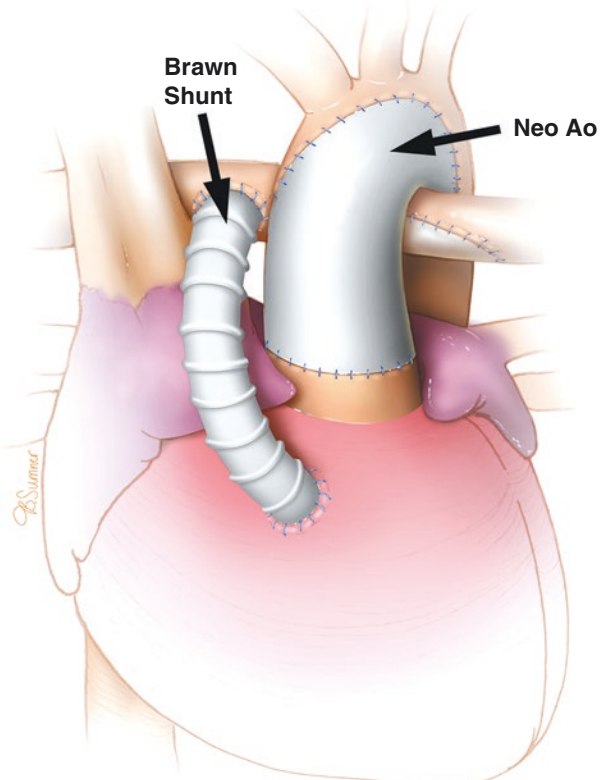

Fig. 11.17 Graphic representation of the Brawn shunt modification of the Norwood procedure. The arrows indicate the ring conduit shunt from the right ventricle into the right pulmonary artery and the reconstructed or neoaorta (Neo Ao). Reproduced with permission from Texas Children's Hospital

stages of the palliative pathway. This is referred to as a comprehensive Stage II procedure. Although the operative mortality with this intervention was initially found to be substantial, mortality has significantly decreased with time as perioperative protocols became available [121]. Depending on institutional experience and preference, the hybrid approach is either reserved for high-risk neonates with HLHS or used liberally as the favored strategy.

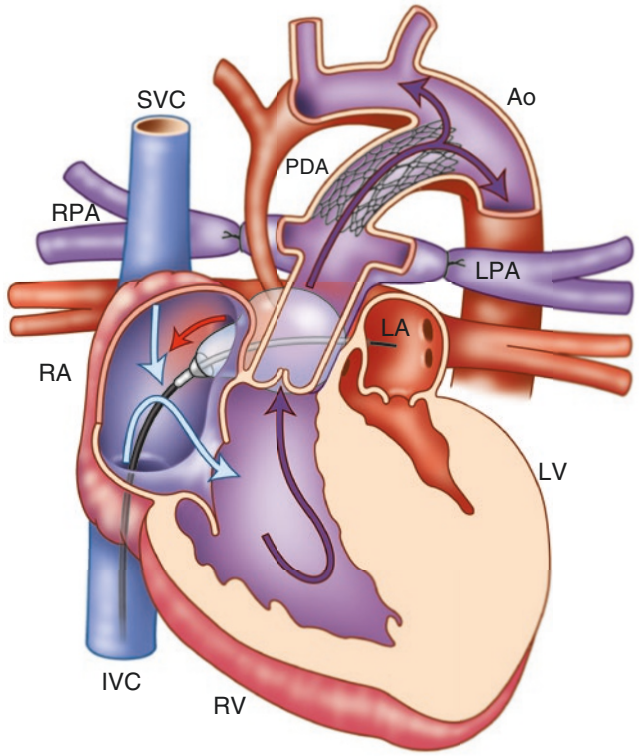

Fig. 11.18 Graphic displaying hybrid palliation for hypoplastic left heart syndrome. The approach consists of ductal stenting, banding of both branch pulmonary arteries, and enlargement of an interatrial communication. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LPA* left pulmonary artery, *LV* left ventricle, *PDA* patent ductus arteriosus, *RA* right atrium, *RPA* right pulmonary artery, *RV* right ventricle, *SVC* superior vena cava

Anesthetic Considerations

It is essential to establish absolutely reliable vascular access and ensure excellent function of all monitors at the outset of the procedure. In the operating room, the management principles discussed previously to maintain systemic output, oxygen delivery, and balance of the Qp/Qs are maintained [122]. Temporary partial occlusion of a branch PA by the surgeon to mechanically limit pulmonary blood flow and favor systemic blood flow is often very useful. Inhalational anesthetic agents or an opioid/relaxant technique may be used as preferred.

The use of an alpha-adrenergic blocking agent (e.g., phentolamine) has been advocated as a means to optimize peripheral vasodilation during the cooling phase of CPB. Long-acting alpha-adrenergic blockade with phenoxybenzamine has also improved systemic oxygen delivery [123]. This is secondary to minimizing regional variations in SaO_2-induced vascular resistance, thereby allowing the use of greater oxygen concentrations to improve systemic oxygen delivery in the postoperative period [124]. The use of TEE is variable among institutions during Stage I palliation. In addition to providing information on anatomy and function, it determines the adequacy of the atrial communication, presence and degree of tricuspid regurgitation, and evaluation of the surgical intervention (Fig. 11.19). It also serves as an intraoperative monitoring tool.

Specific Issues

- *Surgical palliative approach*. The choice of the surgical approach for Stage I palliation (systemic-to-PA shunt or RV to PA conduit) and the perfusion strategy (DHCA or ACP) depend on the surgeon and the center where the procedure is performed [125]. These factors impact the selection of arterial blood pressure-monitoring sites and

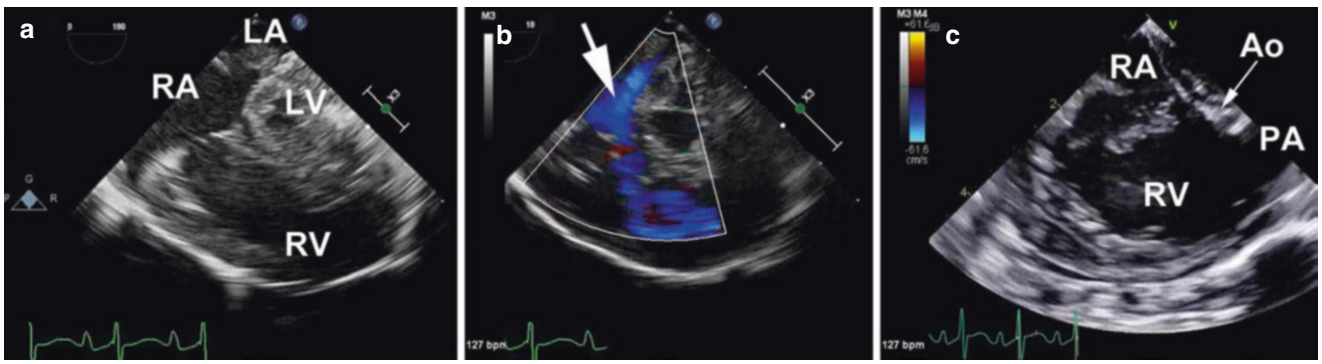

Fig. 11.19 Transesophageal echocardiographic images in hypoplastic left heart syndrome showing a miniscule left ventricle (LV) in the mid-esophageal four-chamber view (**panel a**), flow across the interatrial communication into the right atrium (RA) and right ventricle (arrow) in the same view (**panel b**), and the diminutive native aorta (Ao) and moderately dilated RV giving rise the pulmonary artery (PA) in the mid-esophageal RV inflow-outflow view (**panel c**). *LA* left atrium

may favor the use of cerebral physiologic monitoring. Monitoring procedures must be adapted to the bypass strategy to be used. Whereas a mB-T shunt allows for pulmonary blood flow to occur throughout the entire cardiac cycle (continuous forward flow), in a Sano connection, most of this flow occurs during systole. The narrower pulse pressure and relatively greater diastolic blood pressure due to the lesser diastolic runoff allowed by the Sano conduit as compared with the mB-T shunt is regarded as an advantage for coronary and end-organ perfusion. The Sano strategy is preferred by some to provide a more stable immediate postoperative course. This relatively more favorable circulation is also thought to possibly limit the rates of interstage mortality that occur in these infants while they await a second stage palliation [126]. However, the ventriculotomy required for conduit placement may add to the risk of myocardial injury and the long-term rhythm disturbances. This is a possible disadvantage of this procedure. In a randomized clinical trial of shunt type that included a large number of infants with HLHS undergoing the Norwood procedure, the transplantation-free survival rate at a year post-operation with the RV to PA shunt exceeded that of the mB-T shunt. After that time period, the transplantation-free survival rate was similar in the two groups [125].

- *Right ventricular optimization*. With the RV operating as the systemic chamber in HLHS, all efforts to maintain/enhance RV function during the perioperative period should be considered. Decreased initial stroke distance (distance that blood travels with each heart beat) and cardiac output, as determined by echocardiography, are associated with later mortality or cardiac transplantation. It has been suggested that early evaluation of HLHS patients should include an assessment of stroke distance. Future research should evaluate its value in the postoperative management [127].
- *Balancing the circulations*. After separation from CPB, a balance between the pulmonary and systemic blood flows should be optimized. A conventional management strategy has been to monitor the systemic SaO_2 for this assessment and to guide this balance by targeting a value between 75% and 80%. If this value is less than expected after separating from CPB and potential factors such as inappropriate shunt size and shunt occlusion/distortion have been excluded, steps are undertaken to decrease the pulmonary vascular resistance and increase the systemic arterial blood pressure in order to improve the pulmonary blood flow. A relatively high hemoglobin concentration is important in this setting to enhance the delivery of oxygen and to prevent anemia-related low peripheral vascular tone. At the same time, the deleterious effects of overtransfusion and polycythemia should be considered, particularly in view of the potential negative impact on blood flow across the systemic-to-PA shunt and patency of this connection. If maneuvers that decrease the pulmonary vascular tone are unsuccessful, administration of inhaled nitric oxide as a selective pulmonary vasodilator may be considered. If the SaO_2 is greater than expected, it is reasonable to reduce the inspired oxygen concentration and ensure normocarbia or mild hypercarbia. If there is evidence of adequate systemic output and tissue perfusion, a relatively high SaO_2 may be acceptable. Tracking trends in cerebral oxygenation may facilitate these interventions. A high oxygen saturation combined with a low systemic pressure may also indicate too large an mB-T shunt.
- *Mixed venous oxygen saturation monitoring*. An approach proposed in the neonate with single ventricle physiology after Stage I palliation to ensure systemic oxygenation is the use of continuous mixed venous oxygen saturation (SvO_2) monitoring, using transthoracic oximetric catheters placed by the surgeon at the time of the intervention [128, 129]. One strategy is to target an SvO_2 value >50%, a mean arterial pressure over 45 mmHg, normocarbia, and to administer oxygen as required to maintain the SpO_2 within a desirable range. Relying on SvO_2 as a metric of systemic oxygen delivery has been associated with favorable outcomes in neonates with HLHS [128, 129].
- *Postoperative issues*. Regardless of the surgical technique, patients with HLHS present major challenges of bleeding, myocardial dysfunction, low cardiac output, and hemodynamic instability during the post-bypass period. Other potential problems include renal dysfunction and hepatic impairment [130]. As a result of these concerns, sternal closure may be delayed, and some neonates may need postoperative mechanical circulatory support. Initial studies using signal-processing algorithms of ST segment report success with early detection of events that require rapid intervention to avoid cardiopulmonary arrest. These events were not noticed by conventional ST analysis [131]. Immediate extubation has been proposed to favorably impact outcomes when used judiciously after Stage I Norwood palliation; however, the experience with this practice to date has been extremely limited [132].).
- *Hybrid procedure*. Deferring the risks associated with the Norwood operation to a later time in infancy, by performing a hybrid procedure, can offer potential advantages. Although caring for an infant with HLHS, outside the typical surgical setting, can present major challenges, a report on the anesthetic management of neonates scheduled for hybrid procedure documented relatively stable

intraoperative and early postoperative hemodynamics [133]. Furthermore, most neonates did not require blood transfusions or inotropic support. Performing endotracheal extubation was feasible either at the end of the procedure or soon after the infant was admitted to the intensive care.

Interrupted Aortic Arch

Anatomic Features

Interrupted aortic arch (IAA), a discontinuity of the Ao arch, is an uncommon lesion representing only 1% of all CHD. Affected children have a high incidence of DiGeorge syndrome (22q11 microdeletion).

This anomaly is defined in terms of the site of interruption as follows: type A, if distal to the left subclavian artery; type B, if between the left carotid and left subclavian arteries (most common variant; Fig. 11.20); and type C, if between the carotid arteries. The pathology commonly is associated with a posteriorly malaligned VSD, resulting in the obstruction of the LVOT. Coexisting anomalies include a right Ao arch, aberrant origin of a subclavian artery, TA, and aortopulmonary window.

Pathophysiology

Patency of the ductus arteriosus is essential for survival in this anomaly, as it allows for systemic perfusion. The neonate with IAA presents with congestive heart failure, poor perfusion, and cardiovascular collapse or shock after constriction of the ductus arteriosus and occasionally with differential cyanosis. Thus, the physiology resembles that of severe CoA. The presence of a VSD can cause pulmonary over-circulation and the associated consequences.

Management

After the diagnosis is established, stabilization of the infant is critical; PGE_1 therapy is initiated to maintain ductal patency [134]. Anticongestive therapy and inotropes are administered as needed. Surgery is undertaken in the neonatal period, typically soon after the diagnosis is made. The aortic arch is reconstructed, the VSD closed, and possible subaortic obstruction is resected [135]. Much less commonly, an initial palliative approach is undertaken with Ao arch repair and pulmonary artery banding (PAB) if a VSD is also present, followed by delayed complete repair later in infancy. If the LVOT obstruction is severe (marked subaortic narrowing, annular, Ao root, and/or Asc Ao hypoplasia), alternate approaches including Ao root enlargement, replacement, or other complex interventions may be necessary. A single ventricle strategy is required in some cases.

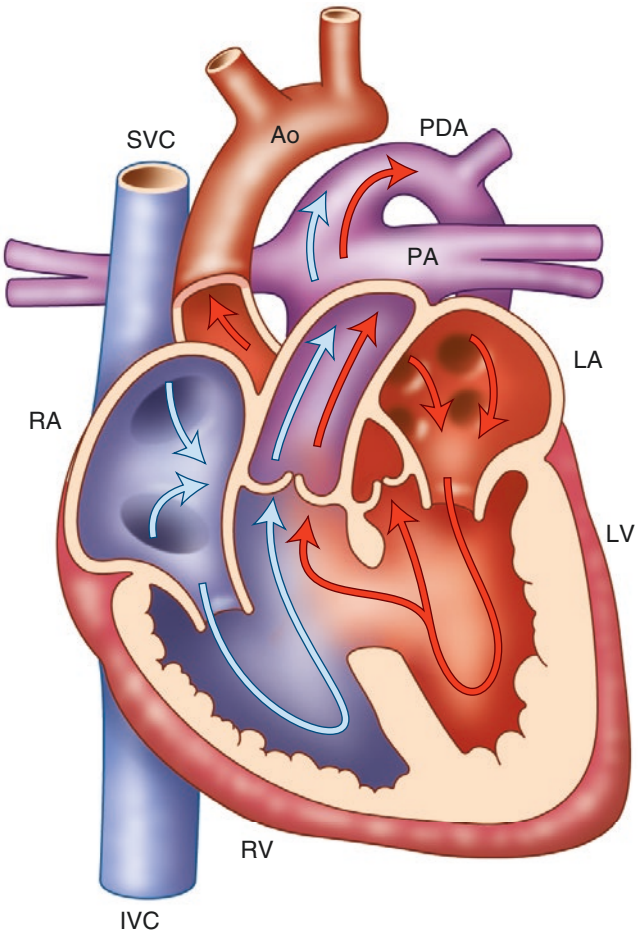

Fig. 11.20 Graphic representation of type B interrupted aortic arch. Note the site of interruption between the left carotid and left subclavian arteries. The patent ductus arteriosus (PDA) supplies the systemic circulation beyond the level of interruption. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle

Anesthetic Considerations

Although echocardiography is diagnostic in most neonates with IAA, additional preoperative studies may be needed to further define the details of the arch anatomy. These examinations in most cases require care at remote locations, adding to the management considerations for the sick infant.

Maintenance of the PGE_1 infusion is critical before the Ao arch is reconstructed. An adequate response generally implies no significant pressure gradient between proximal and distal areas of the interruption. In view of the common association between PGE_1 therapy and complications such as apnea in these neonates, their tracheas are frequently intubated and their lungs mechanically ventilated in the critical care unit.

Specific Issues

- *Monitoring*. It is important to consider the sites to monitor systemic arterial blood pressure and SpO_2 in neonates with IAA [136]. The choice of sites is dictated by the Ao arch anatomy and the presence of coexistent anomalies. In the case of a type B interruption with left Ao arch and aberrant right subclavian artery, for example, none of the vessels that supply the limbs are proximal to the interruption site. Thus, the arterial blood pressure proximal to the site of interruption cannot be measured in any extremity. This is a problem during CPB as the perfusion pressure cannot be recorded from a vessel supplied by a subclavian artery during reconstruction of Ao arch. Monitoring with cerebral oximetry can be useful in this setting. Transcranial Doppler may be used to guide ACP during the reconstruction [137, 138]. SpO_2 in the unrepaired neonate may show differential readings in oxygen saturation, with greater values in the sites supplied proximal to the interruption and reduced values distally reflecting flow from the ductus arteriosus (right-to-left shunting) [136].
- *DiGeorge syndrome*. In view of the potential for developing hypocalcemia in neonates with DiGeorge syndrome, calcium levels should be monitored frequently. In such cases, calcium infusions may be required. The presence of coexisting noncardiac anomalies in this syndrome must be considered including immune deficiency. Irradiated blood products should be used to prevent potentially fatal transfusion-associated graft-versus-host disease.
- *Surgical considerations*. Interventions for IAA can be quite complex, requiring considerable bypass and myocardial ischemic times, particularly when concomitant LVOT obstruction is present. This can be a very challenging condition to manage.

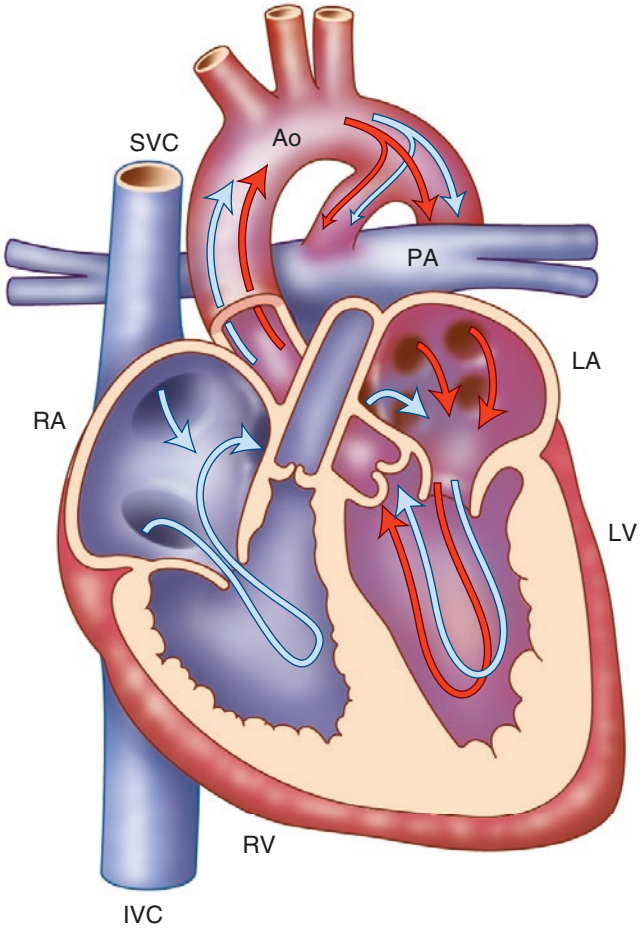

Fig. 11.21 Graphic representation of critical pulmonary stenosis. In this defect, the ductus arteriosus serves as the main source of pulmonary blood flow. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

Critical Pulmonary Stenosis and Pulmonary Atresia with Intact Ventricular Septum

Anatomic Features

Pulmonary stenosis is the most common form of RVOT obstruction among infants, accounting for more than 80% of the cases. This lesion is reported in approximately 10% of patients with CHD. In the classic isolated pathology, leaflet tethering/thickening and commissural fusion lead to the formation of peripheral raphes and narrowing of the valve lumen. Systolic valvar doming is usually identified on cardiac imaging.

Critical PS is the third most common cyanotic congenital disease in the neonate and accounts for approximately 3% to 4% of all congenital lesions diagnosed in infancy [139]. Critical PS (Fig. 11.21) and pulmonary atresia with intact ventricular septum (Fig. 11.22) are lesions characterized by pulmonary valve/RVOT obstruction. The pulmonary valve in the neonate with critical PS, the most severe form of valvar obstruction in infancy, displays fused raphes with a restrictive, eccentric pin-hole size opening. In the uncomplicated or pure form of critical PS, the ventricular septum is intact and an interatrial communication (patent foramen ovale or secundum atrial septal defect) is present. Pulmonary atresia with intact ventricular septum is a lesion characterized by membranous or muscular atresia of the RVOT and wide heterogeneity in the size of the RV cavity and tricuspid valve, infundibular region, and pulmonary arteries.

The tricuspid valve, RV, and pulmonary arteries are frequently abnormal in both of these defects (abnormal tricuspid valve leaflets, tricuspid annular hypoplasia, reduced size of the RV cavity, main and branch pulmonary arteries), but

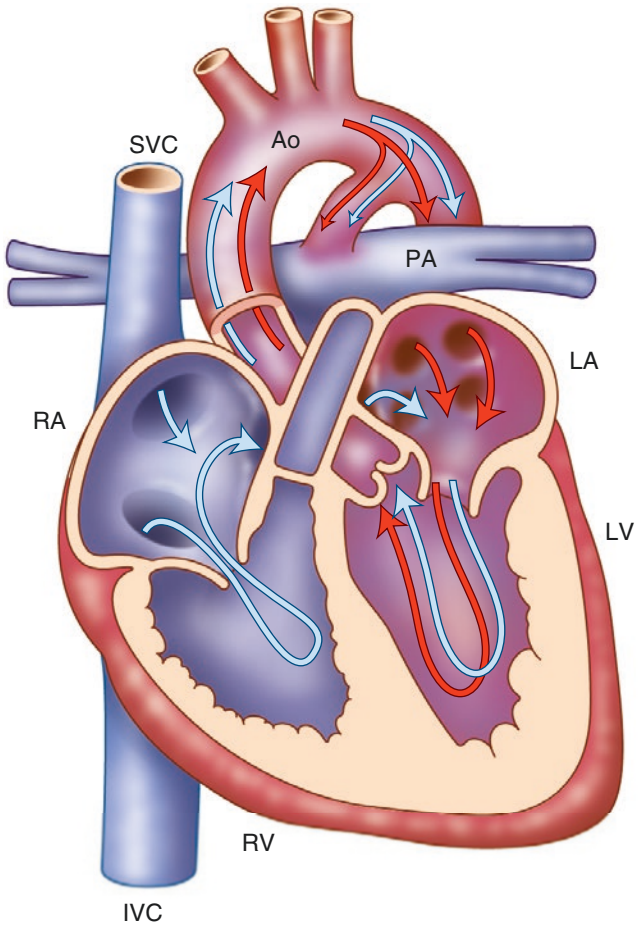

Fig. 11.22 Graphic representation of pulmonary atresia and intact ventricular septum. Note the associated findings in this defect that usually include a patent ductus arteriosus, hypoplastic right ventricle, atrial septal defect, and, in some cases, some degree of tricuspid regurgitation. The ductus arteriosus provides the source of pulmonary blood flow in this lesion. The atrial communication allows for right-to-left shunting. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

they are likely to be of a more severe nature in the neonate with pulmonary atresia and intact ventricular septum.

Pathophysiology

Cyanosis is a common presentation in both of these congenital heart anomalies. The severity of the hypoxemia is determined by the degree to which pulmonary blood flow and the extent of interatrial right-to-left shunting are limited. Affected neonates have ductal-dependent pulmonary blood flow. The severity of the obstruction in critical PS is determined by the extent of valvar narrowing. In pulmonary atresia with intact ventricular septum, no antegrade flow is possible across the valve. The main physiologic consequence of both of these pathologies is an increase in the RV systolic pressure that may exceed systemic values.

In infants with critical PS, the infundibular region (subpulmonary area) hypertrophies, which contributes to the outflow tract obstruction and reduces the RV cavity size. Right ventricular hypertrophy serves as a compensatory mechanism to maintain ventricular output. However, it is associated with diminished RV compliance and diastolic dysfunction. Subendocardial ischemia that results in myocardial infarction and fibrosis impairs systolic function and leads to dilation of the chamber and congestive heart failure in some cases.

In pulmonary atresia with intact ventricular septum, communicating vessels between the coronary arteries and the RV can be present, as may a number of other abnormalities in the coronary circulation. In some cases, the myocardium may rely on coronary perfusion directly from the RV (RV-dependent coronary circulation) [140]. This is a vulnerable situation for the myocardium that can predispose to myocardial ischemia and/or infarction.

In both of these lesions, critical PS and pulmonary atresia with intact ventricular septum and structural abnormalities of the tricuspid valve frequently may lead to tricuspid regurgitation, particularly in the presence of RV hypertension, and RA dilation.

Management

The mainstay of therapy in lesions with severe RVOT obstruction is to stabilize the neonate and institute PGE_1 therapy to maintain a reliable source of pulmonary blood flow via the ductus arteriosus. Options to manage these defects are catheter-based or surgical [141]. Unfavorable anatomy or suboptimal result from a catheter procedure is an indication for surgery. The most common catheter-based interventions are percutaneous PA balloon valvuloplasty and ductal stenting. Surgical options include pulmonary valvotomy with splitting of the commissures and/or partial valvectomy. Concomitantly, resecting an infundibular obstruction or placing a transannular patch may be necessary. In a minority of cases, replacing the valve with an RV to PA conduit is the most suitable option. In rare instances, a systemic-to-PA shunt is required.

In the neonate with pulmonary atresia and intact ventricular septum, angiographic data are obtained before any intervention to determine the presence/absence of communications between the RV and coronary arteries [142]. Potential significant coronary artery abnormalities (fistulae, stenosis, interruptions) also need to be characterized for planning interventional strategies. The concern, once the RV obstruction is relieved, is the potential to develop myocardial ischemia or infarction that is related to reducing the RV pressure

in a patient with RV-dependent coronary circulation [143]. If a patent infundibulum is present and other aspects of the anatomy are favorable, radiofrequency valve perforation and balloon dilation may be undertaken. This procedure has been performed successfully in neonates, allowing antegrade flow into the pulmonary arteries. In some cases, however, the volume of pulmonary blood flow is inadequate, as manifested by significant arterial desaturation upon weaning or discontinuation of PGE_1 therapy. This infant requires a surgical intervention to augment pulmonary blood flow (i.e., an open valvotomy or systemic-to-PA shunt). An approach that combines transventricular valvotomy with a systemic-to-PA shunt promotes growth of right-sided structures, increasing the likelihood of an eventual biventricular repair [144]. Ductal stenting also has been performed in these neonates. Another procedure that may be considered depending on the size of the RV and likelihood of a future biventricular circulation is to reconstruct the RVOT. If anatomic factors such as severely hypoplastic pulmonary arteries preclude a definitive intervention, then palliation consisting of a systemic-to-PA shunt is performed to promote vessel growth. Conditions such as severe coronary obstruction, myocardial ischemia/infarction, and LV dysfunction warrant consideration for cardiac transplantation because of the likelihood of a poor outcome.

Anesthetic Considerations

An important aspect of the care is to ensure patency of the ductus arteriosus by the continuous intravenous infusion of PGE_1. Catheter-based therapy can lead to effective relief of the obstruction, but factors such as abnormal ventricular morphology/geometry, relatively small pulmonary/tricuspid annulus, hypoplasia of the pulmonary arteries, and interatrial right-to-left shunting may not improve the systemic SaO_2 immediately. It is not unusual for the PGE_1 infusion to continue after the procedure is completed. Hemodynamic changes that occur during catheter-based interventions aimed at relieving the RV obstruction are reasonably well-tolerated, providing the ductus arteriosus remains patent and the interatrial communication is adequate to maintain LV filling. This is particularly important during pulmonary balloon valvulopasty. In some cases, depending on the anatomy, ductal stenting may be undertaken. It is well-recognized that catheter-based interventions for these lesions may require repeat cardiac catheterizations with serial dilations and at times even ductal restenting [145]. In infants with pulmonary atresia and intact ventricular septum, the potential presence of coronary abnormalities that may predispose to myocardial ischemia warrants monitoring for this problem. As in the case of all other neonatal cardiac interventions, adequate preparation for these cases is of utmost importance [146].

After surgery that involves relief of the RVOT obstruction, inotropic support should be used judiciously as it can exacerbate the dynamic RVOT gradient, complicating the assessment of the results of the repair. Additional anesthetic considerations apply depending on the planned procedure, approach, and need for CPB.

Specific Issues

- *Suicide right ventricle*. A potential post-procedure problem is that adequate relief of the valvar obstruction, either by a catheter intervention or surgery, can result in a physiology referred to as suicide right ventricle. This results as the hypertrophied infundibulum contracts vigorously and creates significant post-procedural dynamic outflow tract obstruction, in the absence of fixed obstruction. In the case of severe obstruction and associated low cardiac output, therapy with volume expansion and/or beta-blockade may be required. An important goal is to preserve RV function by avoiding significant myocardial depression or increases in RV afterload.
- *Circular shunt physiology*. Another major problem that can occur after these procedures to relieve PS or pulmonary atresia is a circular shunt [143]. This condition is a morbid state in which the presence of a large PDA or systemic to pulmonary shunt after a pulmonary valve intervention is associated with pulmonary regurgitation. This leads to retrograde shunt flow into the RV, which proceeds to the RA due to an incompetent tricuspid valve. Blood then courses across the atrial communication into the LA, LV, and Ao, thus re-entering the shunt. This situation is very precarious because it may lead to significant RV volume overload and a pulmonary steal phenomenon. The unsustainable hemodynamic state requires immediate attention, frequently consisting of escalating support and/or immediate surgical intervention, for survival.

Aortopulmonary Window

Anatomic Features

Aortopulmonary (AP) window, also known as aortopulmonary septal defect, is a rare defect that accounts for only 0.1% of all CHD. This anomaly is characterized by a defect in the wall between the Asc Ao and the PA, creating a communication between these structures (Fig. 11.23) [147]. From an anatomic and physiologic standpoint, this anomaly resembles TA; however, unlike TA, two distinct semilunar valves are present. The size and location of the communication varies, and thus the defect has been classified into vari-

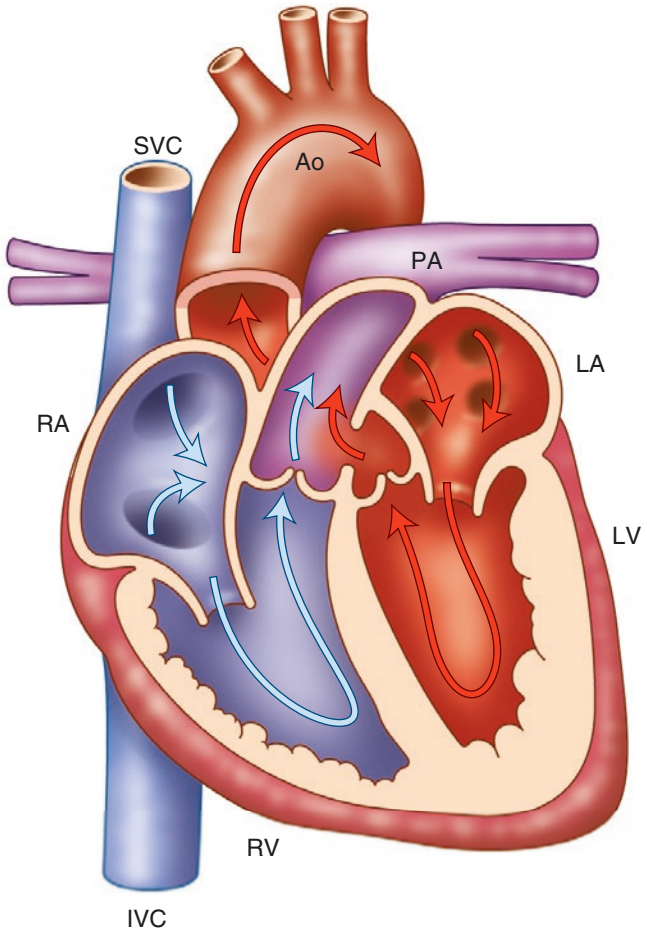

Fig. 11.23 Graphic representation of an aortopulmonary window demonstrating the defect that allows for left-to-right shunting between the great arteries. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

ous types [148]. The lesion can occur in isolation but in most cases is associated with other cardiovascular malformations (PDA, intracardiac communications, TOF, double outlet right ventricle, IAA).

Pathophysiology

The magnitude of the shunt across an AP window depends on the size of the communication, PA pressure, and relative resistances of the pulmonary and systemic vascular beds. Left-to-right shunting across the defect and the increased pulmonary blood flow are associated with increased PA pressures, left-sided volume overload, and congestive symptoms. Furthermore, the large left-to-right shunt at the level of the great arteries can predispose to pulmonary steal, low diastolic blood pressures, and myocardial ischemia. An uncorrected communication can lead to pulmonary vascular disease relatively early in life.

Management

Currently, the favored approach to this lesion is usually surgical, although successful transcatheter closure of the communication has been reported [149]. In most cases, a patch is required to obliterate the defect. Associated pathology is also addressed at the time of surgery.

Anesthetic Considerations

The same anesthetic principles that apply to the management of the neonate with any large vascular communication (e.g., PDA) or any other cardiac defect for which further increases in pulmonary blood flow are detrimental and for which a balance between pulmonary and systemic blood flow should be maintained also apply to this lesion.

Specific Issues

- *Large left-to-right shunt*. The same considerations applicable to other defects associated with a large left-to-right shunt, including the potential for perioperative pulmonary hypertension, apply to AP window.
- *Associated anomalies*. There are a number of surgical techniques that have been applied to the repair of AP window successfully. An important consideration is that the presence of associated anomalies complicates the perioperative course and may contribute to greater early mortality [150].

Ebstein Anomaly

Anatomic Features

Ebstein anomaly represents the most common congenital malformation of the tricuspid valve, but overall, it is a rare anomaly accounting for 0.3% to 0.7% of CHD. It is characterized by the apical displacement of the septal and posterior leaflets of the tricuspid valve towards the RV apex and a redundant, "sail-like" anterior leaflet (Fig. 11.24). The severity of valve displacement and dysplasia varies, accounting for different degrees of tricuspid regurgitation and the diversity of clinical manifestations. The lesion results in an atrialized RV, referring to the region of the RV proximal to the abnormal tricuspid valve attachments. The distal portion of the RV represents the functional cavity. An interatrial communication is present in the majority of affected neonates, and some degree of RV dysplasia and/or dysfunction is usually observed. Other potential associated defects include severe pulmonary stenosis/valve atresia and a PDA. In some cases, the RV output is decreased to such an extent that it is difficult to distinguish between functional and anatomic pulmonary stenosis or atresia. Approximately 10% of patients with Ebstein anomaly have Wolff-Parkinson-White syndrome.

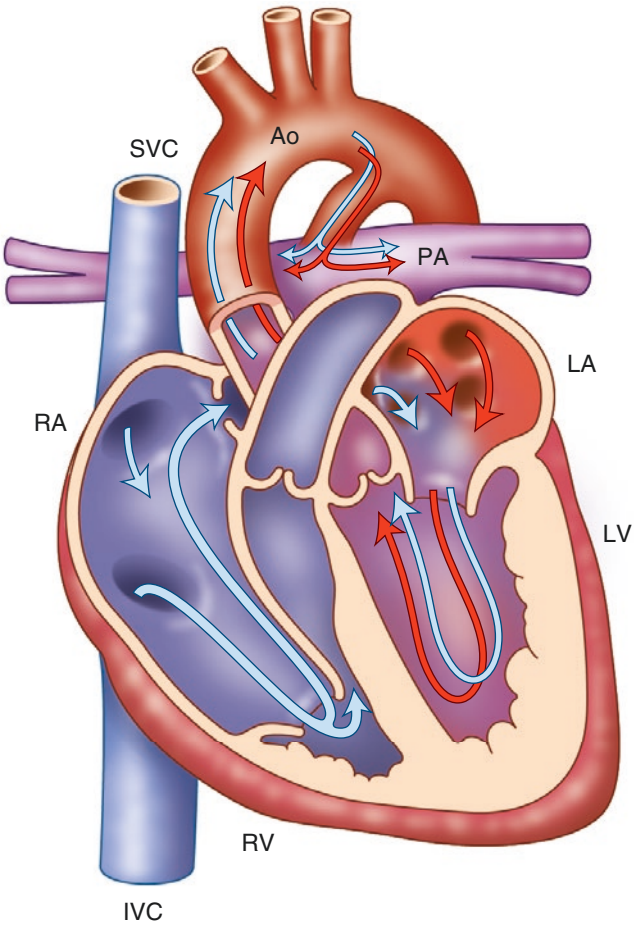

Fig. 11.24 Graphic representation of Ebstein anomaly displaying the displaced tricuspid valve leaflets, associated tricuspid regurgitation, and right-to-left atrial level shunting. In the neonate with anatomic or functional pulmonary stenosis/atresia, a patent ductus arteriosus is the source of pulmonary blood flow. *Ao* aorta, *IVC* inferior vena cava, *LA* left atrium, *LV* left ventricle, *PA* pulmonary artery, *RA* right atrium, *RV* right ventricle, *SVC* superior vena cava

Pathophysiology

Tricuspid regurgitation in this anomaly volume overloads the RV and increases the RA pressure [151]. As the RA pressure increases, it exceeds LA pressure, stretching an existing interatrial communication. This process leads to atrial right-to-left shunting with a decrease in pulmonary blood flow and the appearance of clinical cyanosis. The redundant anterior tricuspid valve leaflet can cause functional obstruction to the RV. Another frequently found feature of the pathology is abnormal RV systolic function. These factors can have detrimental effects on the LV because (1) the dilated and/or dysfunctional RV can impair LV filling and (2) the abnormal interventricular septum can affect LV geometry and systolic function related to ventricular interdependence.

Ebstein anomaly represents a wide clinical spectrum that ranges from minimal or no symptomatology to intractable congestive heart failure and even death. In utero, it can result in fetal hydrops. In fetuses with Ebstein anomaly and tricuspid valve dysplasia, perinatal mortality is high [152]. The hemodynamic status of the neonate is influenced by factors such as the severity of tricuspid regurgitation, presence and degree of RVOT obstruction, size and function of the RV, and associated structural defects (Fig. 11.25). Cyanosis caused by right-to-left atrial shunting under conditions of increased pulmonary vascular resistance is the most common presentation. Severe tricuspid regurgitation almost invariably results in congestive heart failure; if intractable in nature, it can lead to circulatory collapse. A neonatal presentation implies a major clinical problem and generally portends a poor prognosis.

In the neonate with Ebstein anomaly, several additional cardiac problems can complicate the clinical course. Atrial arrhythmias related to atrial dilation or abnormal conduction pathways can occur, and pulmonary stenosis or atresia (either functional or anatomic) can further compromise pulmonary blood flow.

Management

Some neonates require only conservative treatment and follow-up. In the symptomatic neonate, the main problems that require intervention are congestive heart failure and hypoxemia [153]. Diuretic therapy and inotropic support are instituted as needed. Initial hypoxemia after birth can improve as pulmonary vascular resistance decreases, allowing for forward pulmonary blood flow. In cases of severe PS or atresia, an intervention is required. Distinguishing hypoxemia related to increased pulmonary vascular resistance from that resulting from anatomic RVOT obstruction can be difficult. Hence, PGE_1 therapy is frequently instituted to maintain ductal patency until the nature of the hypoxemia can be ascertained or the expected decrease in pulmonary vascular resistance occurs. Initiating other measures aimed at decreasing pulmonary vascular tone and supporting the overall critically ill neonate is warranted.

During the neonatal period, a catheter-based intervention and/or cardiac surgery may be necessary. Catheter therapy targets the relief of RV outflow obstruction and/or to increase pulmonary blood flow (pulmonary valve dilation/perforation, ductal stenting). The selection of surgical procedure is influenced by factors such as details of the anatomy, associated defects, RV size and function, and the clinical status of the neonate. Approaches range from creation of a systemic-to-PA shunt, tricuspid valve repair, palliative surgery anticipating a future single ven-

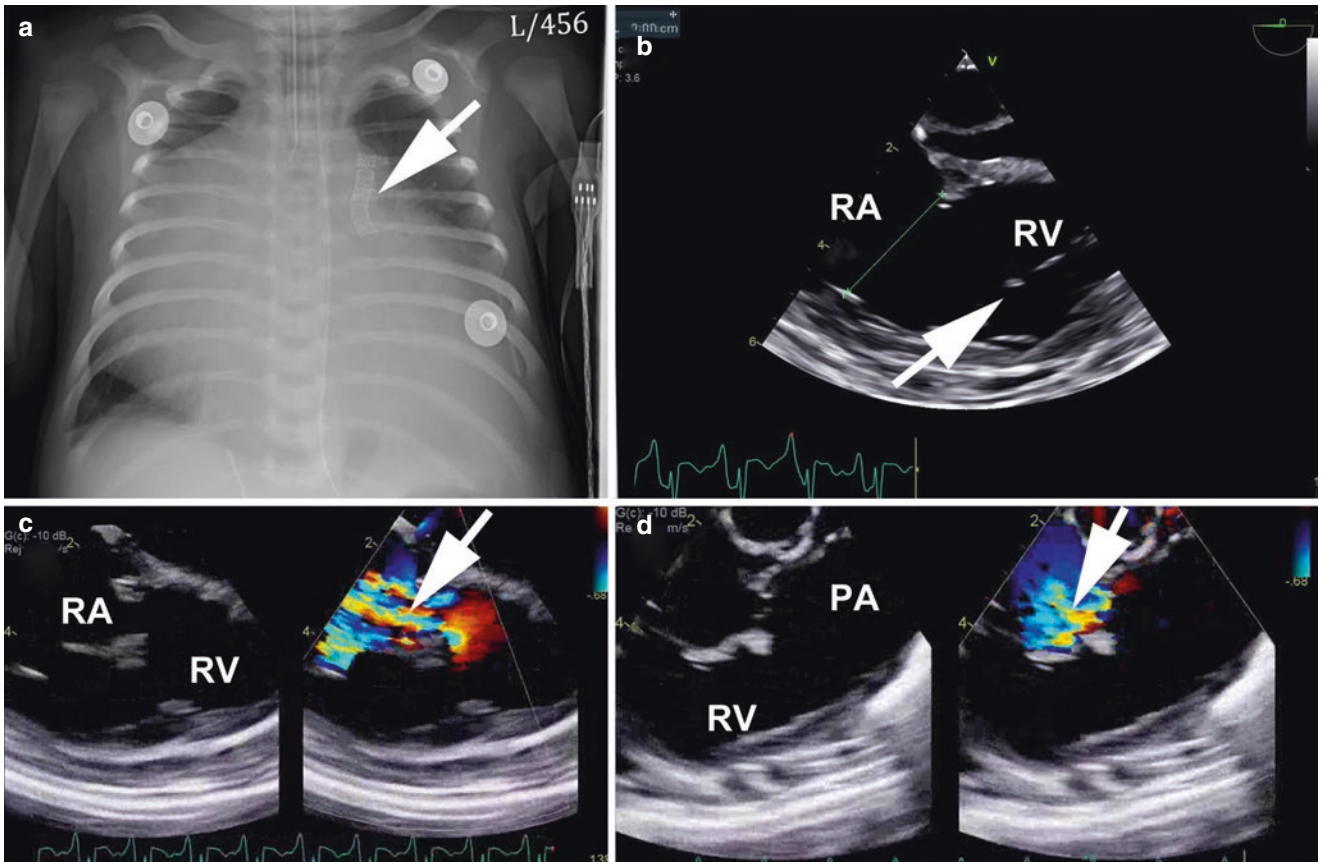

Fig. 11.25 **Panel a**, chest radiograph of newborn with Ebstein anomaly showing severe cardiac enlargement and a stented ductus arteriosus (arrow). **Panel b**, transesophageal four-chamber view showing displaced tricuspid valve leaflets into the right ventricular (RV) apex (arrow) relative to the level of the valve annulus (line), and a moderate to severely dilated RV. **Panel c**, color compare images in equivalent view depicting the wide tricuspid regurgitant jet. **Panel d**, complementary RV inflow and outflow view confirming the severe tricuspid regurgitation (arrow). *PA* pulmonary artery, *RA* right atrium

tricle strategy, and cardiac transplantation. The overall success of the various surgical interventions in the neonatal period has generally been poor in the presence of severe disease [152, 154].

The perinatal mortality rate in neonates with Ebstein anomaly is the greatest within the CHD group, ~45%. The presence of pulmonary regurgitation (e.g., circular shunt physiology), prematurity (<32-week gestational age), larger TV annulus diameter Z-score, and pericardial effusion are strong predictors for mortality.

Anesthetic Considerations

Anesthetic care, when required, is usually for cardioversion, cardiac catheterization, or surgery. The neonate with Ebstein anomaly presents a challenge to the provider of anesthetic care because the infant's clinical status is typically poor and characterized by severe tricuspid regurgitation, cyanosis, congestive heart failure, lactic acidosis, and impending circulatory collapse.

Specific Issues

- *Respiratory status*. Pulmonary mechanics can be compromised by factors such as prematurity, interstitial lung edema, and lung hypoplasia. Mechanical ventilation should be carefully considered while balancing the need to enhance antegrade pulmonary blood flow.
- *Pulmonary vascular resistance*. Increases in RV afterload lead to right heart distention and compromise LV performance. Thus, it is important to optimize not only RV contractility but also to aggressively avoid increases in pulmonary vascular tone that will depress the function of both ventricles.
- *Rhythm disturbances*. Numerous rhythm abnormalities have been reported in these children. Although supraventricular arrhythmias predominate, other abnormalities include atrioventricular block and ventricular arrhythmias. In general, these rhythm disturbances are poorly tolerated and require aggressive therapy that may include cardioversion, the administration of antiarrhythmic drug

therapy, and/or cardiac pacing. Children with Ebstein anomaly and WPW may not tolerate the rapid tachyarrhythmia necessitating radiofrequency cardiac ablation of the accessory pathway depending on the child's condition.

- *Circular shunt*. This physiology can also occur after interventions in this lesion, as described in a preceding section.

Preoperative Assessment of the Neonate with Congenital Heart Disease

History and Physical Examination

It is important for the anesthesiologist to perform a comprehensive preoperative evaluation to identify and plan for factors that could influence the perioperative management. This evaluation begins with a review of the prenatal history including details of the pregnancy, such as maternal illnesses (e.g., diabetes, hypertension), medications, and drug use, as well as a family history of adverse anesthetic events.

Frequently, the diagnosis of cardiovascular disease is established "in utero." Prenatal diagnosis positively influences the preoperative status, resulting in more widespread use of fetal ultrasound to detect cardiovascular pathology [155]. Data regarding fetal studies, if available, should be reviewed. Specific issues of interest beyond details of the anatomy include functional assessment of the cardiovascular system, presence of extracardiac abnormalities, genetic syndromes or other disorders of potential impact, as well as an impression of the overall well-being of the fetus. The issue of associated noncardiac and genetic abnormalities is particularly important given the possible negative effects on clinical outcomes [156].

The child's gestational age is important at the time of surgery as prematurity and low birth weight are also well-known risk factors for morbidity and mortality. An analysis in the Society of Thoracic Surgeons Congenital Heart Surgery Database revealed that even birth during the early term period (37–38 weeks' gestation) is associated with worse outcomes [157]. Relevant information also to be obtained regarding the delivery includes Apgar scores, events that occurred during neonatal resuscitation, and the need for other interventions immediately after birth.

If the diagnosis of heart disease has been made postnatally, details such as clinical presentation, hospital course, and results of all diagnostic studies, which define the cardiovascular abnormalities, interventions performed, and response to these, should be reviewed. It is essential to gather information regarding coexistent medical problems or conditions that could potentially affect other organ systems and impact on the anesthetic management.

The physical examination should note the neonate's weight and length. General appearance should include the level of distress, if any, presence/degree of cyanosis, and overall clinical status. Vital signs, including blood pressure measured in the upper and lower limbs and any gradients between the limbs, should be recorded. The measured SpO_2 at both pre- and post-ductal levels should be noted. A careful examination of the airway and the respiratory and cardiovascular systems should be performed. Respiratory evaluation should note rate and breathing patterns, quality of the breath sounds noting the presence of rales or rhonchi, and the presence of intercostal retractions. If the infant is receiving supplemental oxygen, the inspired oxygen concentration should be recorded. If the airway is intubated, the date when the current endotracheal tube (ETT) was inserted should be noted as well as its diameter, depth at the lips/nose, and the presence/absence of a cuff; any difficulties with blockage of the ETT should be identified, and a recent chest radiograph should also be reviewed. If the lungs are mechanically ventilated, mode and settings should be noted. The cardiac exam should include assessment of precordial activity, heart sounds, murmurs, and gallop rhythms. The presence of any existing vascular access, patency of the catheter(s), size, number of lumens, and appropriateness of catheter tip position should be recorded. Review of medical records and results of previous studies may assist in the determination of vessel patency in the infant with a history of multiple vascular access or catheterization procedures. The abdomen should be examined for the presence of hepatosplenomegaly. Assessment of the extremities should include examination of pulses, capillary refill, skin temperature and color, and overall perfusion.

Approximately 13% of infants with CHD have chromosomal abnormalities. Dysmorphic features or any other noncardiac anomalies that can impact the anesthetic care should be documented. Medications being administered, including indications, doses, and route, need to be reviewed.

Ancillary Studies and Laboratory Data

The preoperative electrocardiogram in the neonate with heart disease allows for assessment of chamber dilation and/or ventricular hypertrophy, rhythm disturbances, and myocardial ischemia (Fig. 11.26). A recent chest radiograph provides information regarding cardiac size and shape, chamber enlargement, and pulmonary vascularity. In addition, it serves to document the position of the ETT tube, stomach tube, and indwelling vascular catheters (Fig. 11.27). The echocardiogram and additional imaging studies obtained (cardiac magnetic resonance imaging, computed chest tomography, cardiac catheterization and angiography) pro-

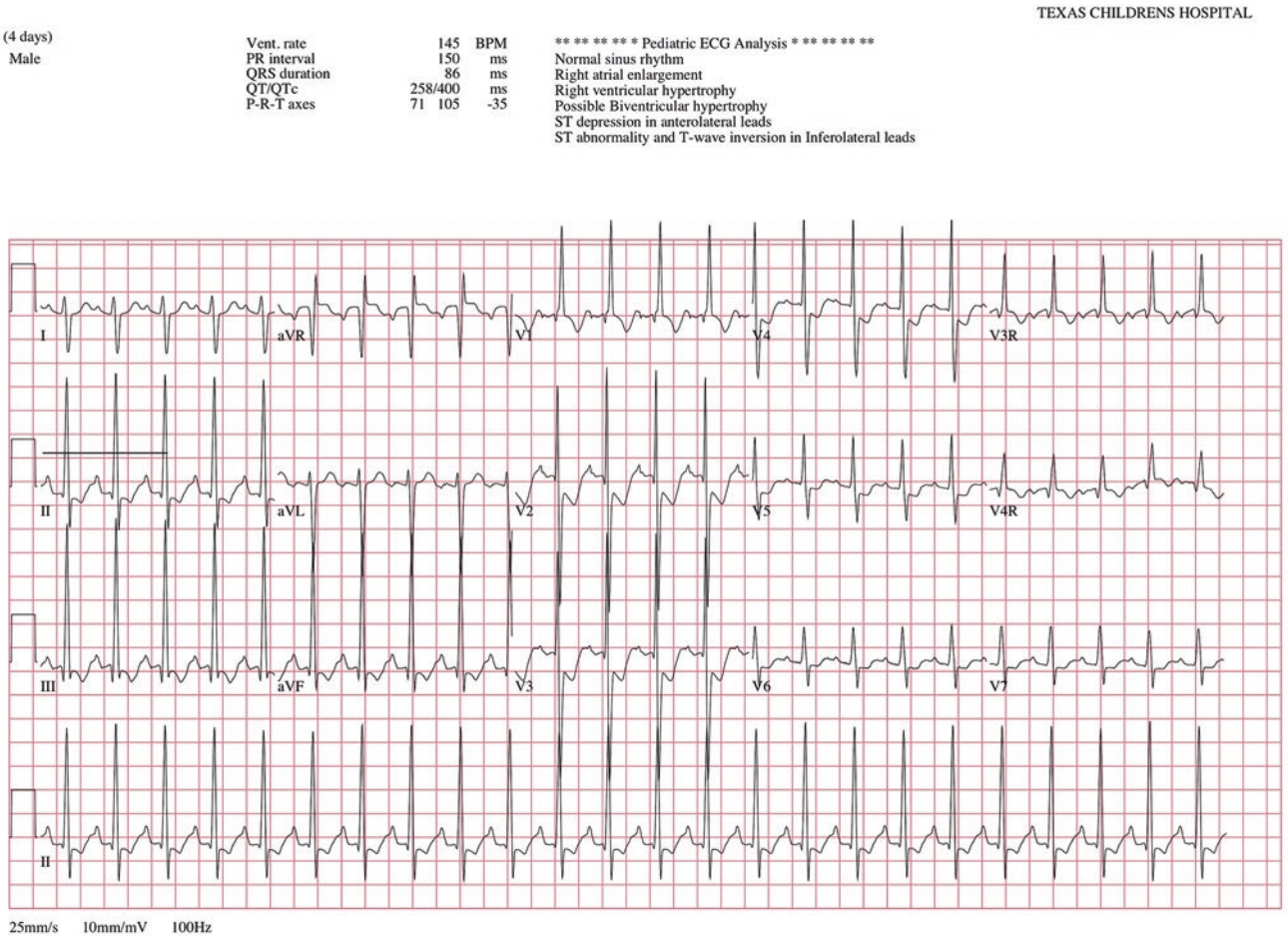

Fig. 11.26 Preoperative electrocardiographic recording in a newborn with truncus arteriosus. Note the peaked P waves in lead II indicative of right atrial enlargement, the prominent precordial voltages consistent with biventricular hypertrophy, and the diffuse ST-T wave changes suggestive of compromised myocardial blood flow

vide important information regarding the structure and function of the heart. All of these studies should be reviewed carefully, and the findings documented.

The complete blood count, electrolyte levels, blood glucose, renal/hepatic function tests, and coagulation studies [prothrombin time, partial thromboplastin times, and international normalized ratio (INR)] should be reviewed. The most recent blood gas analysis should be examined to assess oxygenation, ventilation, acid-base status, and lactate values. The results of any other investigations that may have been performed (e.g., head ultrasound, brain magnetic resonance imaging, renal ultrasound) also should be reviewed.

Informed Consent

The preoperative visit allows the anesthesiologist an opportunity to meet the family, discuss the anesthetic plan, and address questions in preparation for the procedure. A surgical intervention in a neonate with cardiac disease may imply a substantive risk of morbidity and even mortality. In addition, the anesthetic care for cardiac surgery also entails greater risks when compared with other neonatal surgeries [95, 158]. Although it may not be possible to specify the contribution of anesthesia itself to the overall risks of the procedure, it is reasonable to discuss the most likely potential anesthetic problems that may be encountered perioperatively.

Over the last several years the subject of potential detrimental effects of general anesthesia on the developing brain has received increasing attention [159, 160]. This concern was initiated by observations made in small animal models and subsequently in nonhuman primates implicating nearly all anesthetic agents [161–163]. The issue triggered a number of studies and resulted in heated controversy on the subject [164–169]. A multidisciplinary effort, SmartTots, was launched accordingly to address the issue of anesthetic safety in young children [170, 171]. Led by this concern and before the availability of clinical trials, the US Food and Drug

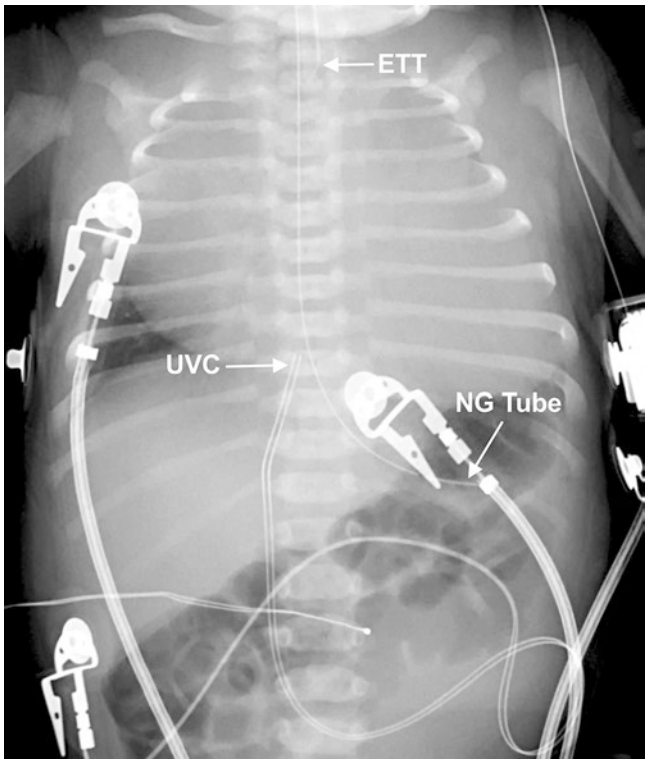

Fig. 11.27 Radiograph in a neonate with congenital heart disease displaying massive cardiomegaly. The position of the tip of the endotracheal tube (ETT) appears high, prompting readjustment. The nasogastric (NG) tube is the stomach and the tip of the umbilical venous catheter (UVC) is in good position at the inferior vena cava to right atrial junction

Administration issued a warning in 2016 on the use of anesthetic agents in young children [172, 173]. This was followed by changes in informed consent requirements at several local levels to include disclosure of this potential risk to parents [174]. Although subsequent human studies, including randomized controlled trials, have been less concerning [175–177], the warning is still in place and further research continues to be advocated [178–180].

Cardiac surgery in the neonate is a major undertaking regardless of the nature of the procedure, and one must always expect the parents to be apprehensive and concerned. In some cases, particularly those with a postnatal cardiac diagnosis or if the infant had been previously discharged from a well-baby nursery, significant parental stress can be present. The preoperative consultation provides an opportunity to defuse parental anxiety, answer questions, and reassure the parents regarding the unwavering commitment of the entire perioperative team towards a good perioperative outcome.

Fasting Period

The established preoperative fasting guidelines for surgery in neonates should be followed, which may vary among countries. Although in recent years these have tended to become more liberal [181], the gastric emptying times are prolonged in those with CHD [182]. A significant number of infants receive maintenance intravenous fluids preoperatively. Adequate hydration is particularly important in the presence of obstructive pathology, cyanotic disease, or single ventricle physiology, as optimizing the ventricular preload can limit potential detrimental hemodynamic changes associated with anesthesia and surgery.

Perioperative Considerations in the Neonate Undergoing Cardiac Surgery

Anesthesia for cardiac surgery in the neonate should be delivered by highly skilled individuals with expertise in the various forms of pediatric heart disease. This requires knowledge of the wide spectrum of anatomic and physiologic abnormalities involved, the natural history of congenital defects and other conditions that affect the cardiovascular system, possible management strategies, and overall short- and long-term outcomes. A comprehensive understanding of the disease process, hemodynamic perturbations, and how they are influenced by the anesthetic and surgical procedure are of outmost importance. Familiarity with the anticipated perioperative course, including potential problems and complications, is essential. In addition to these cognitive skills, the care of small infants with critical heart disease requires consummate technical proficiencies. The ability to communicate clearly and work effectively with other members of the team is also key to achieving the best possible outcome.

Transport to the Operating Room

Most infants who require cardiac surgery within the first few weeks of life are cared for in a critical care setting, either in a neonatal or cardiac unit. The collaborative effort of members of the unit's multidisciplinary team strives to maintain and optimize vital organ function until the planned intervention. At the time of transport, excellent communication between the care providers and the operating room team must be assured in order to address any recent changes in the neonate's clinical status, current therapy, and any other relevant issues. This handoff process is critical so that all relevant information can be conveyed between providers. The implementation of the I-PASS (illness severity, patient summary, action list, situation awareness and contingency plans, and synthesis by receiver) for the transfer of patients between units and teams has been shown to result in improved transfer efficiency, safety, and satisfaction of providers and families [183]. During transport, the main considerations include temperature homeostasis, adequate airway support/ventilation, careful maintenance of necessary infusions, and availability of emergency airway

equipment and drugs. Be aware that essential drug infusions can be compromised by kinking of the lines or alterations in the height of the delivery systems. In some cases, a self-inflating bag, air tank, or oxygen/air blender system is needed to deliver room air or a specific inspired oxygen concentration between room air and 100% oxygen. Monitoring the vital signs and systemic oxygen saturation is essential during transport. For those in whom the levels of oxygenation and ventilation are critical factors, the use of a transport ventilator may be preferable to manual ventilation.

Premedication

The need for premedication is rarely, if ever, indicated in the neonate because this age group is not at risk to experience separation or other forms of anxiety. On rare occasions, premedication can minimize metabolic stresses and facilitate the placement of intravenous access in the agitated or struggling infant. Specific concerns, such as the potential for hypercyanotic spells in tetralogy, also may warrant the judicious use of premedication. Close observation including SpO_2 monitoring and oxygen administration as needed is recommended after premedication.

Intravenous Access

Absolutely reliable intravenous access is mandatory to administer fluids, blood products, and medications during surgery. In most neonates with heart disease, a peripheral or indwelling intravenous catheter is already in place when they arrive in the operating room, facilitating an intravenous induction of anesthesia. In the neonate without intravenous access, consideration should be given for securing peripheral access before induction of anesthesia. The size of the catheter and need for more than a single site of access should be determined by the infant's clinical status and nature of the intervention. When placing an intravenous cannula in a very small infant, the use of a fine guide wire as the catheter is advanced can ensure a very reliable intravascular route. Never rely solely on the integrity of an intravenous access route that arrives with the child! In many institutions peripherally inserted intravenous catheters (PICC lines) are the sole forms of access in sick neonates. While these catheters are suitable for the administration of maintenance fluids and other clear fluid infusions, in general they are not appropriate for boluses because of the small diameter of the lumen(s) and length of the catheter.

In all neonates, the potential for right-to-left shunting across a patent foramen ovale or the presence of any intracardiac communication mandates the meticulous removal of air from all injections and the intravenous infusion tubing. Air filters can be difficult to use in the intraoperative setting because they can limit the speed at which boluses of intravenous fluids, propofol, and blood products are administered, although they can be useful for clear fluid and drug infusions as well as in the preoperative and postoperative periods.

Availability of Emergency Medications

In view of the potential for sudden hemodynamic compromise in the neonate with CHD, drugs for emergency situations should be prepared in anticipation of the procedure and be immediately available to the anesthesiologist delivering the care. It is essential for these drugs to be at hand during transport to and from the operating room or any other setting where anesthetic care may be provided.

Physiologic Monitoring

The selection of monitors is guided by the child's clinical status and the nature of the planned procedure. In addition to routine monitors, the intricate nature of cardiac surgery mandates the need for additional monitors as outlined in the sections that follow.

Electrocardiography

Five-lead electrocardiography during cardiac surgery is used to assess heart rate, cardiac rhythm, and ST segments. In most cases, leads II and V5 are displayed on a monitor, and tracings from other leads can be examined as needed. Changes in heart rate can be caused by hypoxia, light anesthesia, stimulation, hypovolemia, or the surgical dissection. Abnormalities in cardiac rhythm can result from hypoxia, electrolyte imbalance, acid-base abnormalities, intravascular/intracardiac catheters, and surgical manipulations within the thorax. Ischemia may be evident on direct examination of the electrocardiographic tracing or ST-segment analysis.

Pulse Oximetry

Monitoring the SaO_2 is essential during cardiac surgery. The need for sampling at various sites is dictated by the anatomy and pathophysiology. SpO_2 monitoring serves as an indicator of intracardiac or great artery level shunting and of pulmonary blood flow. In addition to providing continuous assessment of SaO_2 and heart rate, the SpO_2 waveform can be used as a surrogate of the adequacy of peripheral perfusion and cardiac output [184]. It is wise to place backup sensors, which can be used if the primary sensors fail. Ensure that the sensors are well protected from extraneous light and direct pressure.

Capnography

Capnography confirms proper placement of the ETT, the adequacy of ventilation, and pulmonary blood flow. It also

facilitates the recognition of acute problems that can influence lung compliance. End-tidal carbon dioxide ($ETCO_2$) monitoring provides a gross index of pulmonary blood flow and can be useful during cases in which it may be altered. A specific example of its use is during PAB, at which time the $ETCO_2$ can be a useful guide of optimal occlusion. A caveat in interpreting capnography occurs in cyanotic heart disease, during which $ETCO_2$ measurements can underestimate $PaCO_2$ values owing to altered pulmonary blood flow and ventilation-perfusion mismatch [185, 186]. $ETCO_2$ may be used to track changes in any of the above variables even in cyanotic heart disease provided it is standardized against a blood arterial carbon dioxide value at baseline. In neonates, $ETCO_2$ may underestimate the true end-tidal carbon dioxide tension because of the neonate's small tidal volumes, dilution of end-tidal gases with fresh gases, and large end-tidal gas sampling rates (see Chap. 7).

Temperature

Temperature is monitored routinely during all cardiac procedures. In cases requiring CPB, temperature is sampled at multiple sites. The most common sampling locations include the nose, rectum, bladder, esophagus, and skin. The objective is to measure core (central), peripheral, and possibly, brain temperature, given that hypothermia during bypass has a major role in organ preservation. Temperature monitoring is also essential to ensure that the neonate has been cooled for a sufficient period before initiation of circulatory arrest or related bypass strategy. Similarly, temperature must be assessed during the warming period. Although hypothermia is frequently used during neonatal interventions, failure to re-establish normothermia when coming off bypass increases oxygen consumption and may induce an acidosis, as well as cause detrimental changes in hemodynamics and the coagulation status. Be aware that the rectal temperature may be influenced by the cooling blanket temperature in small infants, unless a small pad is interposed.

Arterial Blood Pressure

Noninvasive Monitoring

A blood pressure cuff of appropriate size is used in all neonates undergoing cardiac surgery to allow automated measurements, regardless of the presence of an indwelling arterial catheter. This offers an alternate option to measure blood pressure in the event the arterial line malfunctions. A second site also enables determination of gradients between upper and lower extremities, depending on the pathology or surgical procedure. The selection of suitable monitoring sites is influenced by the underlying anatomic abnormalities and the history of prior surgical interventions (e.g., mB-T shunt, arterial cutdown, subclavian flap aortoplasty).

Indwelling Arterial Monitoring

Because of the involved nature of cardiac surgery in the neonate, invasive arterial pressure monitoring is warranted in virtually every case. In addition to measuring the blood pressure on a continuous, beat-to-beat basis, it allows for frequent blood sampling to determine the hematocrit, acid-base status, PaO_2 and $PaCO_2$, blood glucose, calcium levels, and electrolyte values.

Sites for Invasive Monitoring

A variety of different sites may be used to invasively monitor the arterial blood pressure in the neonate, each with specific advantages and disadvantages. Umbilical artery blood pressure monitoring is unique to the neonate. Catheter placement in this vessel is often possible during the first few days of life. The tip of the umbilical arterial catheter should be positioned between T6 and T10 (high position) or between L3 and L5 (low position). Advantages of umbilical artery access include relative ease of placement and reliability of access as there is a low likelihood for a catheter in the Ao to be "positional" or subject to the problems that can affect peripheral arterial catheters (vasospasm upon placement, vasoconstriction after CPB). In general, umbilical artery catheters provide optimal tracings of arterial blood pressure and facilitate blood sampling. Complications include potential obstruction of blood flow to specific beds (e.g., renal), distal emboli, thrombotic complications (e.g., mesenteric, Ao, renal artery), and infection. Indwelling catheters have also been associated with necrotizing enterocolitis and problems during enteral feedings in the neonate [187]. Monitoring the blood pressure via an umbilical arterial catheter is not recommended beyond 7–10 days of life.

The radial artery is the usual site to monitor invasive arterial blood pressure in the neonate. It can be accessed percutaneously with a 24 or 22 gauge catheter depending on the size of the neonate, often using a Seldinger technique. This can be facilitated by ultrasound guidance if necessary [188, 189]. Radial arterial tracings are very occasionally dampened after CPB, rendering blood pressure assessment unreliable during this critical period. This situation can be resolved by having the surgeon place a small recording needle into the Asc Ao. For a more stable setup, a pressure-monitoring catheter can be attached to a stopcock integrated into the arterial pressure transducer tubing. Vasospasm also can hinder obtaining accurate blood pressure measurements throughout the case; however, this is rare. This problem may be solved by infusing lidocaine or papaverine through the arterial catheter.

Before inserting a radial arterial catheter, one should review the anatomy and planned operation. In the case of a CoA, right radial artery catheter placement is preferred, as it reflects proximal Ao pressure perfusing the brain and coronary arteries, and the tracing will not be lost if the surgeon has to clamp the left subclavian artery. Monitoring at this site

also can guide management of regional cerebral perfusion if this strategy is used (discussed later in the chapter). If an aberrant or retroesophageal right subclavian artery is present and the use of TEE is planned, cannulating the right radial artery is discouraged; the tracing will likely be dampened or flat after the imaging probe is inserted into the esophagus due to compression of the vessel. If the surgical plan involves placing a mB-T shunt, an arterial catheter in the ipsilateral side of the graft would not be advised because the blood pressure may not be measurable during portions of the procedure as the vessel is temporarily occluded. Furthermore, measurements obtained after opening of the shunt may not be accurate.

The ulnar and the radial arteries constitute the dual blood supply to the hand. The radial artery usually is preferred over the ulnar because avoiding the ulnar artery allows preservation of a larger contributor of blood supply to the hand. The ulnar artery often is the larger vessel, and it alternatively can be cannulated for monitoring invasive arterial blood pressure. The Allen test to assess the distal adequacy of collateral circulation of the hand as a measured of radial or ulnar patency is difficult to apply, inconclusive, and not generally performed in neonates. A modification of the test can be performed by observing for changes in the hand pulse oximetry signal while occlusive pressure is applied to one or the other artery.

Some practitioners find that cannulation of the ulnar artery is easier than accessing the radial artery, particularly in infants with Down syndrome. This group, known to have a high incidence of CHD, can present challenges during percutaneous radial artery cannulation [190]. Because of the risk of ischemia to the hand, placement of a catheter in the ulnar artery is not advisable if the radial artery is thrombosed or after attempts at cannulation have been made. Despite concerns of distal ischemia, a report in the literature indicates a similar risk for ulnar, radial, and femoral arterial lines [191].

The brachial artery has been considered an end artery without collateral circulation. Because of concerns for distal limb ischemia, this site is not usually recommended to establish arterial access. However, it has been used extensively in some centers without sequelae. For example, in one institution where the brachial artery was the second choice for arterial cannulation (after the radial artery) in neonates and infants, there were no major complications in 386 patients who underwent brachial artery cannulation [192].

Femoral artery cannulation is also used in neonates undergoing CPB as an alternative site (see Chap. 7). Catheters 2.5 Fr, 5 cm long, have been used in neonates [193]. In one report of 282 infants (median age 10 weeks), of whom 98 were neonates, pulse discrepancy between the lower limbs and loss of a pulse occurred more frequently with catheters larger than 2.5 Fr and after prolonged use. All of these issues resolved in 100% of instances. The reported rate of arterial injury after femoral artery cannulation is 2%. In a retrospective review of 66 children with arterial injury [194], complications were attributable to ECMO far more than other reasons for arterial monitoring; only one (4-year-old) child sustained an ischemic injury after femoral artery cannulation for monitoring.

The foot arteries (dorsalis pedis and posterior tibial vessels) can be considered as alternate sites for blood pressure monitoring. Although they may not be the first option (for arterial cannulation), they can be quite useful during surgery when bypass or hypothermia is not planned, or for monitoring in the intensive care unit. Disadvantages of these sites include a high incidence of failure of the catheter to reliably display central Ao pressure after hypothermic CPB and a somewhat greater pressure recorded from these sites as compared with central pressure due to pulse wave amplification. The latter issue can confound the interpretation of blood pressure gradients in some cases.

The right temporal artery historically was used for monitoring arterial pressure in neonatal intensive care units. The only time it should be considered for arterial access in the modern era, if at all and after the risk-benefit ratio has been carefully assessed, is when all other sites do not allow for the arterial blood pressure of interest to be monitored (i.e., CoA or IAA with an aberrant subclavian artery that arises distal to the coarctation or interruption). In these situations, the temporal artery provides the only monitoring site that reflects the Asc Ao pressure perfusing the brain and coronary arteries. The very serious concern related to temporal artery catheterization is the fact that emboli can be introduced into the cerebral and ophthalmic circulations by even minute volumes of flush fluid. Serious neurologic injury and blindness are well-documented complications of the use of this site [195].

Cutdown for Arterial Cannulation

If percutaneous arterial line placement is unsuccessful, arterial cannulation via surgical exposure of the vessel can be performed. At some centers, a cutdown is performed primarily or very early in the process of gaining arterial access. Advantages of a surgical cutdown include speed of placement and direct visualization of the artery/catheter during cannulation, minimizing trauma to the vessel, creation of a false lumen, or formation of a hematoma. Disadvantages include possible damage to the vessel caused by scarring. If the radial artery is accessed by cutdown, the time for Doppler-detected flow to resume in the vessel after decannulation is prolonged. It can also be difficult to cannulate the same vessel during future interventions.

Central Venous Pressure Monitoring

Central venous access provides for monitoring of the central venous pressure (CVP) and also for delivery of vasoactive agents safely and expeditiously into the central circulation. It can also be useful for intravascular volume replacement and the administration of blood products. Caution should be exer-

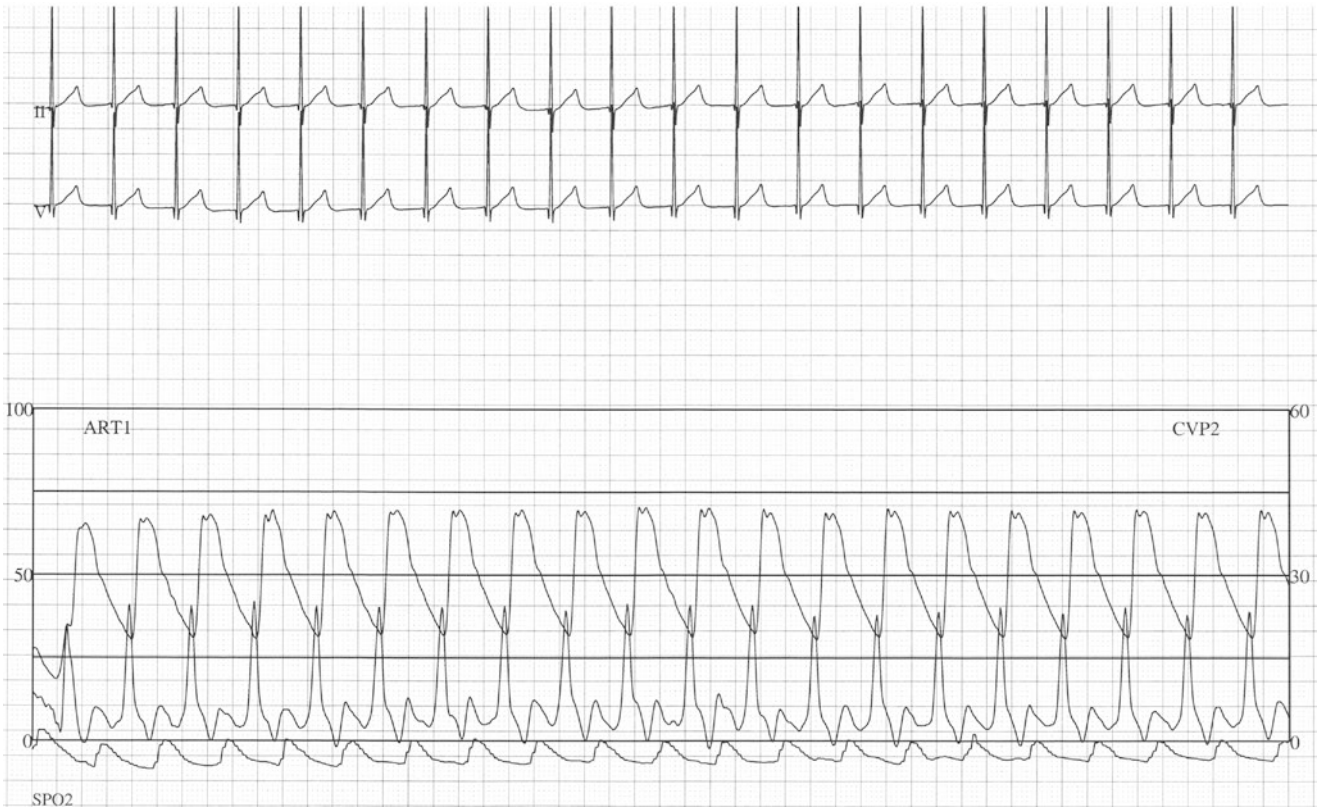

Fig. 11.28 Intraoperative recording in a neonate during junctional rhythm. Note the absence of P waves on the electrocardiographic leads II and V in the *upper panel*. The *lower panel* displays superimposed systemic arterial and central venous pressure tracings. Tall cannon atrial waves ("A" waves) are seen in the central venous pressure tracing corresponding to atrial contraction during ventricular systole against a closed tricuspid valve. The bottom tracing in the lower panel corresponds to the pulse oximeter tracing

cised in delivering fluids or blood products rapidly via a central line as this route leads directly to the heart! Complications may arise if the fluids are inadequately warmed or if the potassium concentration is increased. In addition, the venous pressure tracing can facilitate the recognition of an abnormal rhythm (e.g., junctional rhythm, Fig. 11.28), the "fine-tuning" of pacemaker settings, and the recognition of inadequate venous drainage [e.g., SVC drainage in the case of a catheter in the internal jugular vein]. Increased CVP pressure may also indicate a problem with the venous cannulae of the CPB circuit. Sampling from the SVC also can be obtained to measure SvO_2 and used as a surrogate of cardiac output and oxygen delivery. In general, the catheter with the smallest diameter possible should be used for percutaneous access. The length of insertion varies according to the site of placement [196]. In some cases, direct transthoracic placement of catheters may be favored. The position of the tip of the CVP catheter should always be assessed on the postoperative radiograph. It should not extend beyond the junction of either the SVC or IVC with the atrium to avoid the possibility of cardiac perforation and tamponade (since the junction is the limit of the pericardium).

Ultrasound Guidance

The success rate and safety of central venous cannulation can be markedly improved by the use of imaging techniques (Fig. 11.29) [189, 197]. Various ultrasound modalities that include audio Doppler and two-dimensional imaging assisted by color flow/spectral Doppler have been applied with good success. Real-time ultrasound guidance improves the success rate, decreases the procedural time, and reduces the rate of complications associated with cannulation of the internal jugular vein [198–200].

Percutaneous Sites for Central Venous Access

Several sites in the neonate are available for central venous access. In addition to the challenges imposed by the small size of the vessels in the young infant, factors such as venous anatomy, vessel patency/prior attempts, hydration status, and operator skill/experience all influence the success of cannulation. Preferred sites vary according to institutional preference; in most cases, the femoral vein and internal jugular vein are favored.

The umbilical vein can be cannulated during the first few days after birth and can provide useful access to the central

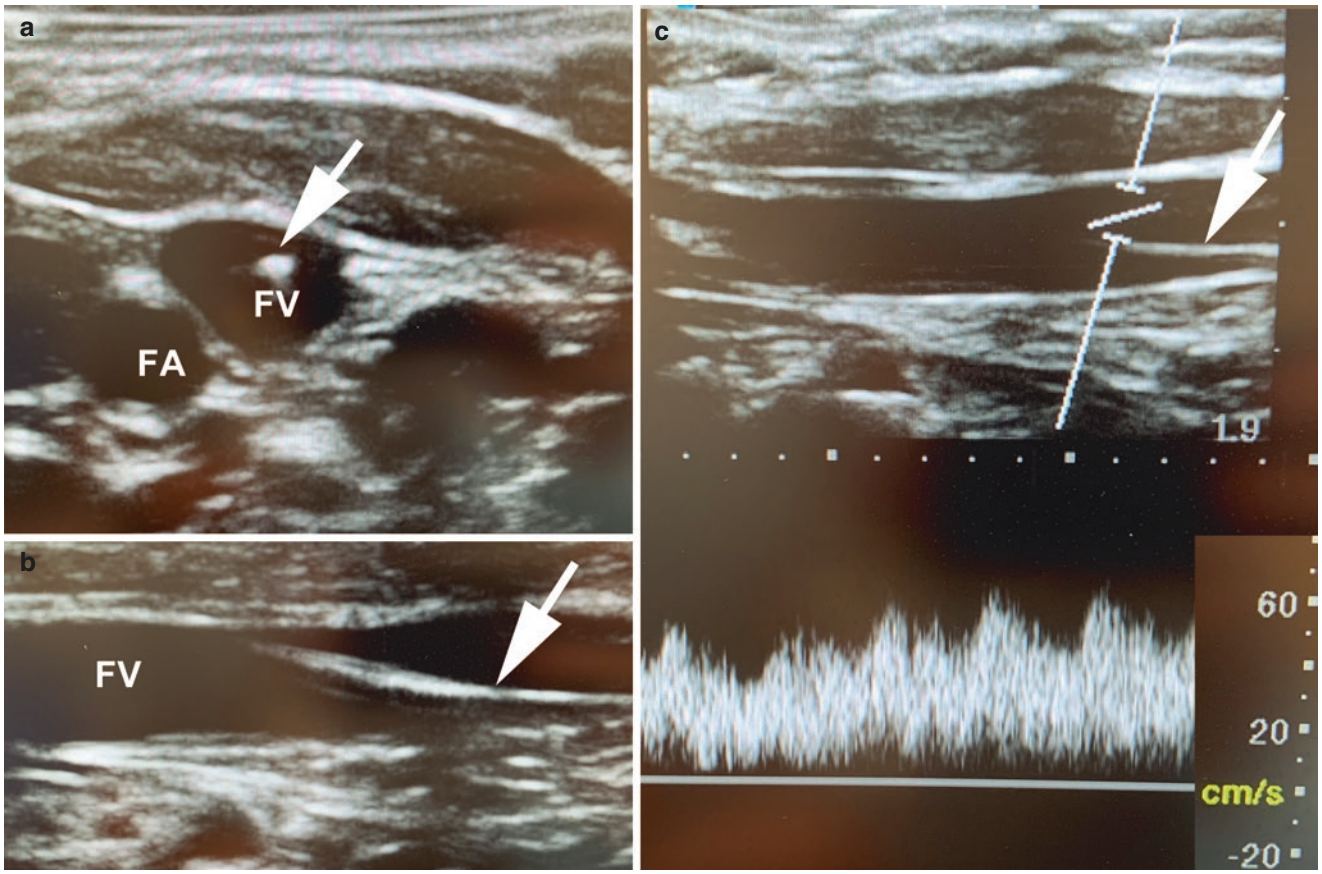

Fig. 11.29 **Panel a**, short-axis image obtained during ultrasound-guided right femoral venous (FV) access depicting the location of a catheter within the vein (arrow). **Panel b**, corresponding long-axis view confirming wire position (arrow). **Panel c**, pulsed-wave Doppler interrogation showing phasic low-velocity flow (<60 cm/s) in the cannulated vein. The wire is noted by the arrow. *FA* femoral artery

circulation. As the catheter is advanced, it can be threaded either into the hepatic veins or through the ductus venosus into the IVC. It is important to document the position of the catheter tip by radiography or ultrasonography. If the catheter has entered the IVC, its tip can be seen above the level of the diaphragm on a radiograph. This is the optimal position as the catheter can be used to monitor CVP and deliver medications directly to the heart. If the tip of the catheter is located within the liver, it may not provide an accurate measurement of the CVP, and delivery of vasoactive medications can cause complications (e.g., liver necrosis and portal vein thrombosis). In this case, an alternate site should be considered for the central venous catheter. A clear advantage of cannulating the umbilical vein is that other venous sites are preserved for future interventions. This is especially important for the neonate with planned staged palliation and anticipated serial cardiac catheterizations, for which venous cannulation is paramount. Umbilical venous catheters generally can be left in place for up to 2 weeks.

The femoral vein is another site to site for placement of a central venous catheter in the neonate (see Chap. 7). In fact, the femoral vein is favored in many centers as opposed to the internal jugular vein in infants who weigh less than 4 kg. Cannulating the femoral vein obviates the need to place a catheter in the SVC and decreases the likelihood of problems such as stenosis and/or thrombosis that can result from cannulating the internal jugular vein in small infants. Patency of the SVC is crucial in infants with single ventricle physiology for whom a superior cavopulmonary anastomosis is part of the palliation pathway. Infection is a rare complication of femoral venous cannulation, but the rate of infection is comparable to that of other sites in children [201].

The internal jugular vein is a very common site for central line placement in children undergoing cardiac surgery and is also commonly used in neonates. The main advantage of the internal jugular route is the direct path between the vessel and the RA. However, disadvantages of this site in the neonatal age group include (1)difficult cannulation due to the small size of the vessels, which are relatively small structures in a tiny infant, with little margin for error; (2) increased risk of carotid artery puncture; (3) the possibility of SVC complications (thrombus, narrowing); (4) potential for vessel or cardiac puncture and less tolerance for hemodynamic compromise as compared with older children; and (5) risk of

lung puncture and development of pneumothorax. The routine use of ultrasound to locate the vessel is strongly recommended. In some cases, the right internal jugular vein can be quite small compared with the left internal jugular vein. This may indicate the presence of a persistent LSVC.

The external jugular vein is sometimes very easy to visualize and to puncture. It is often possible to pass a catheter centrally through the external jugular vein with a small diameter "J wire." This route tends to be overlooked but is often successful and less likely to result in complications than repeated attempts at a difficult internal jugular puncture [202, 203].

The subclavian vein also can be used for central venous access in the neonate. Cannulation of the left subclavian vein generally is preferred over the right because the angle taken as the vessel continues into the innominate vein and enters the SVC is less acute than on the right, and, therefore, the end of the catheter is less likely to be against the wall of the vessel causing potential injury [189]. This site might be preferred over the internal jugular approach as it may be more stable. Disadvantages of subclavian venous line placement include a greater potential for pneumothorax, inability to apply pressure at the vascular entry site, and tendency for malposition (contralateral brachiocephalic vein or the ipsilateral internal jugular vein) [204]. A catheter in the subclavian vein also is more likely than a catheter in another site to kink or malfunction with placement of a sternal retractor.

The use of the brachiocephalic vein for central venous cannulation has been reported to be highly successful (see Chap. 7), even in preterm infants, when guided by supraclavicular ultrasound [205].

Direct Transthoracic Pressure Monitoring

In some cases, transthoracic pressure-monitoring catheters (e.g., in the RA, LA, PA), as well as those with oximetric capabilities, are placed by the surgeon under direct vision while the sternum is open, usually near or after separation from CPB. This route offers the only approach in some cases to monitor pressure in a structure of interest (e.g., LA, PA). LA pressure measurements can assist if poor LV function is anticipated and in the presence of decreased ventricular compliance or mitral regurgitation. The use of transthoracic PA pressure monitoring has decreased over the years, but certain cardiac pathologies in the neonate continue to have a significant potential for acute pressure increases after repair (e.g., obstructed TAPVR, TA). In these (types of) settings, the presence of a PA pressure catheter can be useful for postoperative management. In addition to monitoring pressure depending on the location of the catheter, the PA catheter can be used to infuse drugs and volume, as well as monitor SvO_2 saturation. Extreme care must be taken to ensure that emboli (e.g., air) are not introduced to LA catheters.

A benefit of transthoracic-placed catheters is that they preserve other sites for future percutaneous vascular access and reduce complications associated with placement. The main concerns of these types of lines, however, are bleeding, particularly upon removal, and inability to compress the site. Chest drainage tubes are usually maintained well after the catheter has been removed to avoid accumulating blood, which may lead to cardiac tamponade. In rare cases, the presence of the catheter against the endocardial surface of the heart can trigger ectopy or sustained arrhythmias.

Urinary Output Measurements

Cardiac surgery involves fluid shifts, blood loss, and alterations in systemic perfusion that can impact renal blood flow/function. Thus, urine output is routinely measured in most cases, particularly when the intervention is taking place over a protracted period. Urine output provides a useful index of the adequacy of renal perfusion and cardiac output. For infants, the use of a miniature-graduated burette makes it possible to record small urinary volumes. Although the presence of urine output is reassuring, no specific value is necessarily predictive of good renal function postoperatively. In some cases, the neonate receiving chronic diuretic therapy may require larger drug doses intraoperatively to augment the urine output. Factors such as the use of cardioplegic solutions that may include agents such as mannitol or furosemide can also influence urine output.

Transesophageal Echocardiography

Intraoperative TEE provides real-time information about cardiac anatomy and function during surgery (Fig. 11.30) [206]. It is particularly valuable to confirm the adequacy of surgical repair, detect residual shunts, evaluate valvar competence, determine outflow patency, and examine ventricular function [207]. If significant hemodynamic abnormalities

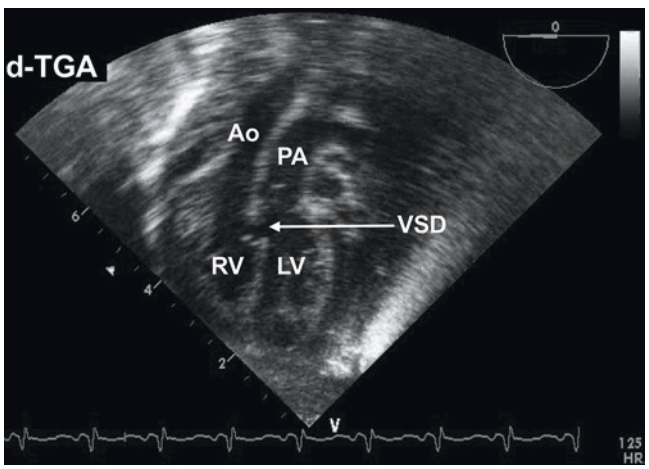

Fig. 11.30 Preoperative deep-transgastric transesophageal echocardiogram in a neonate with *d*-transposition of the great arteries (d-TGA) and a ventricular septal defect (VSD) undergoing complete repair. *Ao* aorta, *LV* left ventricle, *PA* pulmonary artery, *RV* right ventricle

are identified in the immediate bypass period, revision of the repair can then be undertaken [208].

At the time of this writing, two multiplane TEE imaging probes of differing transducer tip size are available for use in the neonate, one referred to as a micro or neonatal probe and the other as the mini or pediatric probe. Both devices incorporate full capabilities for two-dimensional imaging, spectral and color Doppler, and M-mode echocardiography. Data regarding the safety of TEE in the pediatric age group demonstrate a large margin of safety and a small incidence of complications, in the range of 1% to 3% [209]. However, the small infant should be very carefully monitored for evidence of cardiorespiratory decompensation during passage and manipulation of the TEE probe [210, 211].

Neurologic Monitoring

Infants and children undergoing congenital heart surgery are at risk for neurologic and behavioral impairment [212–214]. In contrast to embolic episodes, which affect adults undergoing cardiac surgery, global cerebral hypoxia and/or ischemia is the primary etiology of neurologic dysfunction in infants and children, thus the value of multimodal brain monitoring in the form of near-infrared spectroscopy (NIRS), transcranial Doppler ultrasound, electroencephalography, and bispectral index electroencephalography (BIS). These may minimize the potential for neurologic morbidity and optimize outcome [215–222]. Specific applications of neurologic monitors include determining the maximum acceptable duration of circulatory arrest and minimum acceptable bypass flow rates.

Near-Infrared Spectroscopy

Near-infrared spectroscopy is a noninvasive technology used to monitor regional cerebral tissue oxygenation (rSO_2; Fig. 11.31) [223]. When the NIRS probe is placed on the forehead, it directs a light source through the skull and brain tissue that is then sensed by different detectors (shallow and deep). The optical principle relies on the distinct absorption

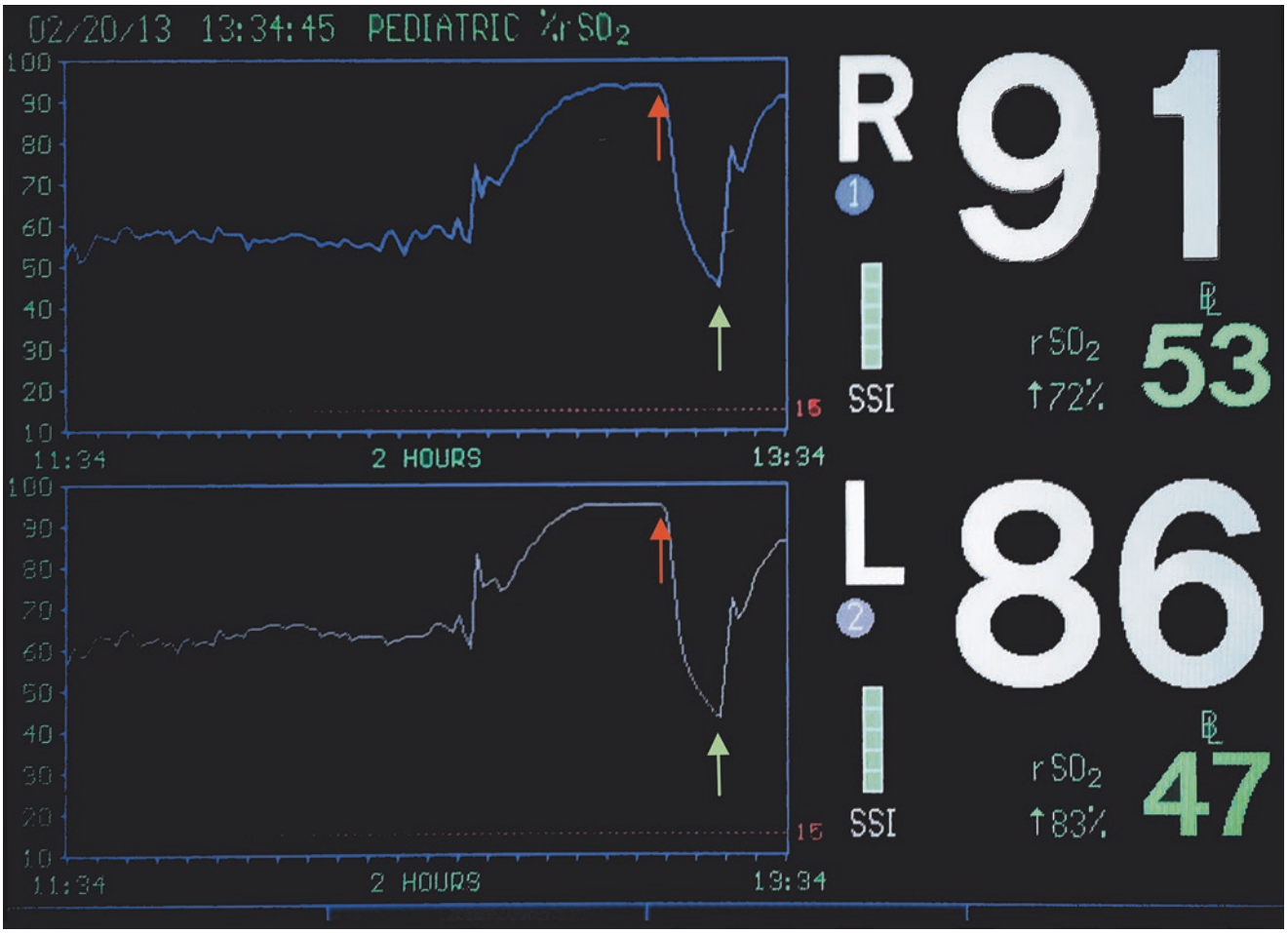

Fig. 11.31 Near-infrared monitor tracings displaying right (R) and left (L) cerebral oxygen saturation (rSO_2) during neonatal cardiac surgery. The red arrow marks the initiation of deep hypothermic circulatory arrest and the associated decrease in rSO_2 in both hemispheres. As bypass pump flows are re-established (green arrow), the rSO_2 increases. A very brief period of low pump flows results in a transient drop in the rSO_2

spectra of hemoglobin species. The wavelengths of infrared light that are used measure the concentrations of oxygenated and deoxygenated hemoglobin in order to determine rSO_2. Online trend monitoring of this parameter then provides indirect information on the adequacy of cerebral oxygenation, a surrogate of cerebral perfusion, allowing opportunities for intervention if critical values are detected. In contrast to SpO_2 values which reflect saturation in the arterial component of the circulation, the measured rSO_2 combines the saturations in both the arterial and venous blood, an issue considered a limitation of the technologyor aortic clamp in non bypass cases.

This type of cerebral oxygenation monitoring has been advocated for most neonatal cardiac cases but is particularly effective during Ao arch reconstruction using bypass techniques that involve regional cerebral perfusion [138, 224, 225]. It is also known to aid in recognizing problems such as the malposition of bypass cannula or aortic clamp in non bypass cases that can result in neurologic injury if not detected [226]. Treatment algorithms for low NIRS have been developed for use during congenital heart surgery [227]. Ongoing experience continues to accumulate with respect to the contributions of this technology to perioperative care [215, 218, 219, 228].

Although NIRS monitoring is increasingly being used, it may not yet be part of the standard of care in all centers that specialize in the management of infants and children with heart disease [222, 229, 230]. To this date no randomized controlled trials have evaluated the clinical benefits of NIRS monitoring in the neonate with CHD and to definitively prove a benefit in outcome. Cerebral oximetry also has been recommended for routine use in the postoperative period after cardiac surgery in view of the observation that infants with prolonged, low rSO_2 demonstrate a greater incidence of periventricular leukomalacia [220, 227, 231]. This condition can contribute to impaired neurodevelopment [220, 232].

Transcranial Doppler Ultrasound

Transcranial Doppler ultrasonography (TCD) has been used as a monitor of cerebral blood flow velocity and microemboli during cardiac surgery [233, 234]. The technique for flow assessment uses pulsed-wave ultrasound at 2 MHz and provides peak systolic and mean flow velocities (expressed in cm/s) (Fig. 11.32). Cerebral blood flow velocity in the neonate is monitored using a temporal window or open anterior fontanelle with insonation of the middle cerebral artery.

In neonates, TCD has been used to determine the threshold for detectable cerebral blood flow during low-flow bypass. During the arterial switch operation using alpha-stat arterial blood gas management, 30 mL/kg/min was the threshold for detectable cerebral perfusion in this population [235]. In neonatal Ao arch reconstruction during the Norwood operation, a mean bypass flow of 63 mL/kg/min maintained both rSO_2 (using cerebral oxygenation) and blood flow velocities (using TCD) within 10% on the baseline [236]. This represented sufficient but not excessive cerebral perfusion.

TCD can detect and quantify cerebral emboli, the latter identified as high-intensity signals (HITS) on a display. Data regarding the use of TCD to detect cerebral emboli during cardiac surgery in infants and children is somewhat limited, although one study demonstrated that microemboli could be detected in the carotid arteries of children during congenital heart surgery, particularly immediately after Ao unclamping [237]. However, interpretation of the Doppler signals was confounded by a variety of artifacts. No correlation was identified between the number of emboli detected and acute postoperative neurologic injuries. Currently, TCD monitoring is reserved for special indications by some centers and is not considered a standard monitor for routine use.

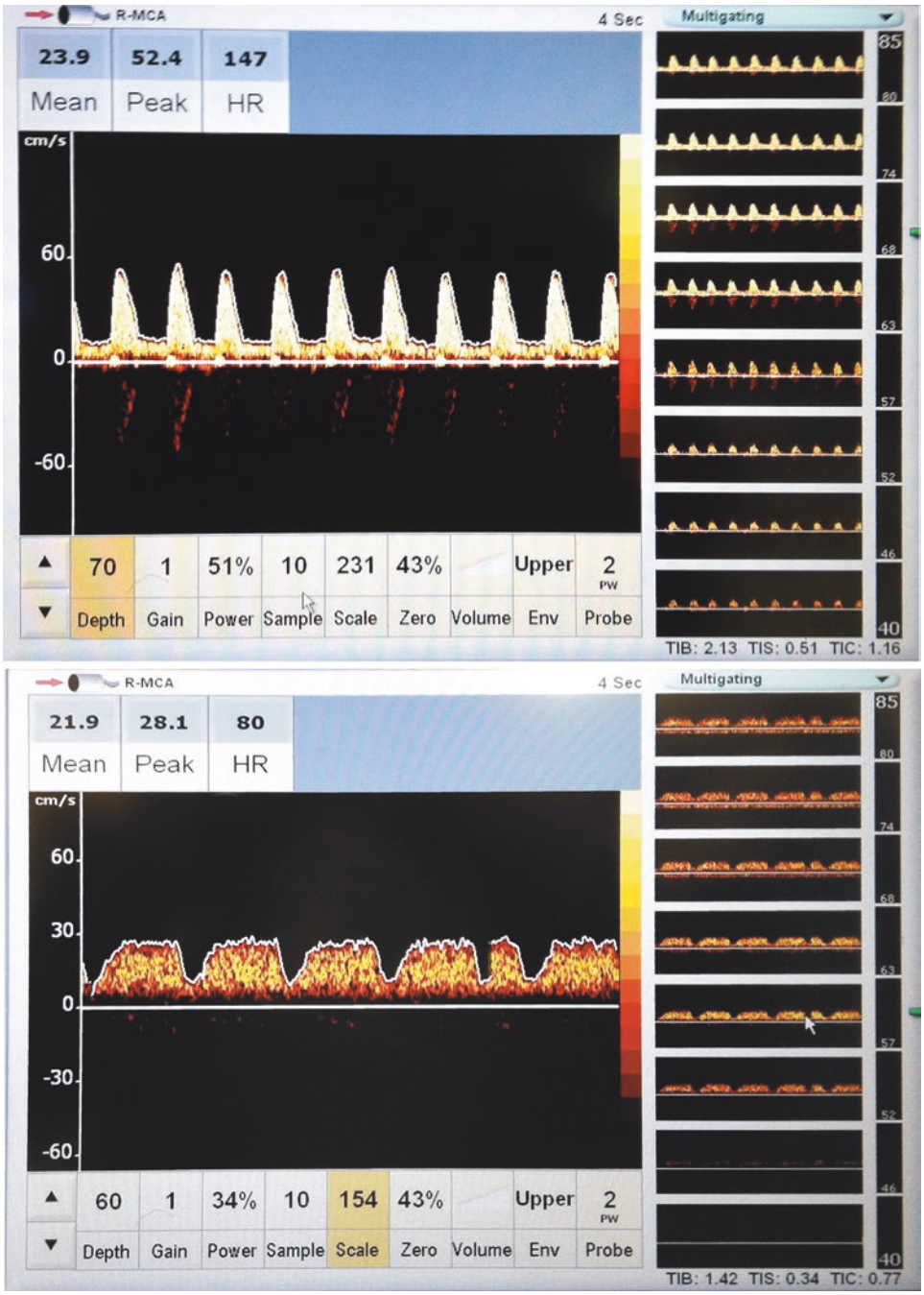

Fig. 11.32 Transcranial Doppler ultrasonography directed to sample flow across the right middle cerebral artery. The signals were obtained with probe placement over the anterior fontanelle in a neonate undergoing cardiac surgery. The upper panel displays the tracing during the pre-bypass period and the lower panel during cardiopulmonary bypass. Note the different characteristics of the corresponding flow patterns

Intraoperative Management of the Neonate Undergoing Cardiac Surgery

Induction of Anesthesia

Induction of anesthesia in the neonate usually is accomplished via the intravenous route, which is preferred over the inhalational route because the former enables the airway to be rapidly secured without the use of cardiac depressant drugs and, hence, provides a greater margin of safety. The presence of shunts can impact the kinetics of intravenous agents; a large left-to-right shunt can prolong induction of anesthesia because the drugs are recirculated through the lungs. Hence, a less concentrated amount of anesthetic agent reaches the brain, delaying the onset of anesthesia. In contrast, a large right-to-left shunt speeds an intravenous induction because a significant portion of the drug bypasses the pulmonary circulation and directly enters the systemic circulation, rapidly reaching the brain.

In the neonate, intravenous access usually is present preoperatively. If this is not the case, access can be established before

induction, or if this is not possible a carefully titrated inhalation induction and early placement of an intravenous catheter can be performed. Inhalational anesthetics dilate vascular beds and reduce sympathetic tone. Although these are desirable goals in general, the effects can be detrimental in the neonate with decreased myocardial performance who requires an increased resting sympathetic tone to maintain systemic output.

In general only carefully titrated concentrations of inhalational anesthetic agents are used during neonatal cardiac surgery. Be especially aware of the danger of controlling ventilation during induction with anything but a minimal concentration of a inhalational agent. Three factors independently and substantively affect the uptake and distribution of inhalational anesthetics in neonates: the presence of a shunt (right-to-left or left-to-right), the solubility of the inhalational anesthetic, and a decrease in cardiac output. See Chap. 3 for a full discussion of the pharmacokinetics and pharmacodynamics of inhalational anesthetics in neonates with CHD.

An important goal of the anesthetic management in the neonate with heart disease undergoing surgery is the selection of drugs that have the least impact on the cardiovascular system in order to maintain adequate cardiac function and ensure systemic oxygen delivery. A technique that combines several agents (balanced technique) with minimal myocardial depressant effects traditionally has been used for induction of anesthesia in order to limit the extent of cardiac depression. Titrated doses of an opioid and non-depolarizing muscle relaxant are commonly used. A benzodiazepine also can be added. It is important to emphasize that even the smallest dose of an opioid can depress cardiac function in the critically ill neonate because opioids can reduce the release of endogenous catecholamines. Therefore, it is imperative to monitor carefully and intervene promptly if decompensation occurs.

Maintenance of Anesthesia

After induction, anesthesia can be maintained with an inhalation anesthetic, an intravenous technique, or a combination. For many years, a large-dose, synthetic opioid-muscle relaxant technique was used because it minimally decreases cardiovascular function and offered significant benefits by blunting the physiologic stress response [238, 239]. However more recently clinical practice has changed; many centers now favor inhalational anesthetics as the primary agents and a limited opioid dose. Contemporary data support this approach. The use of large-dose opioids with the goal of providing "stress free" anesthesia is not an important determinant of early postoperative outcome [240]. At the same time, when inhalational anesthetics are properly used (e.g., isoflurane or sevoflurane), they do not significantly reduce the cardiac index in children with CHD [241]. The potential benefit of anesthetic preconditioning of the heart continues to be investigated, with no particular anesthetic agent as yet proven to be superior in this role in humans [242]. As mentioned, the use of nearly all anesthetics and sedatives with the exception of opioids and dexmedetomidine has been associated with neuroapoptosis and neurodegenerative changes in animal studies.

During the last several years the use of dexmedetomidine has significantly increased in pediatric cardiac surgery [243, 244]. Initially, the use of the drug was reserved for infants beyond the neonatal age group, although the use of dexmedetomidine in neonates has been increasing over the last several years. The clearance of dexmedetomidine in term neonates is significantly diminished and increases rapidly in the first few weeks of life, reflecting the relative immaturity of the metabolic processes in the neonatal period (see Chap. 3) [245]. This issue warrants consideration when infusions are used. A dosing strategy of dexmedetomidine in infants undergoing cardiac surgery with CPB suggested that its clearance was reduced after CPB for >1 h, leading the authors to recommend that the infusion rate be reduced in neonates after bypass [246]. In the same study, the incidence and severity of arrhythmias, hypotension, and excess sedation were similar to those published previously. In addition to decreasing the opioid and benzodiazepine requirements, dexmedetomidine offers several benefits including prophylactic and therapeutic effects for reentrant supraventricular tachycardia, attenuation of renal injury, and neurologic protection [83, 247–251].

It should be emphasized that no regimen or combination of anesthetic agents has proven to be superior for all neonates with CHD. The most appropriate technique for each infant and each cardiac lesion must be considered individually. The main goals of the anesthetic management are to optimize systemic oxygen delivery, protect and maintain ventricular function, and ensure the adequacy of cardiac output.

Cardiopulmonary Bypass in the Neonate

Pre-bypass Period

After monitors have been applied and anesthesia induced, the neonate is positioned for the procedure. In most cases, after arterial access is established, baseline measurements of blood gases, acid-base status, hematocrit, glucose, and calcium levels, and the activated clotting time (ACT) are documented. This is the optimal time for transesophageal imaging in order to avoid interference from electrocautery once the operation commences. Vigilance is of utmost importance during this phase of surgery because of the potential for blood loss, rhythm abnormalities, compression of cardiac and vascular structures, and several other factors that can impact hemodynamic stability.

The neonate should be very carefully monitored during dissection around the heart. Sometimes it is necessary to alert the surgeon to pause activity and allow time for the heart to recover if function appears compromised. Alternately,

minor changes in cardiac function have to be accepted if the procedure is to be performed! The anesthesiologist should constantly watch the progress of surgery to integrate the physiological changes observed on the monitors with the actions of the surgeon.

Perfusion Equipment, Tubing, Circuits, and Bypass Prime

Neonatal cardiac surgery frequently requires the use of CPB [252]. During full bypass, all the systemic venous blood is directed to the extracorporeal circuit; in contrast, during partial bypass, only a portion of the systemic venous return is captured in the venous reservoir and the remainder reaches the beating heart. Ventilation is required during partial bypass for gas exchange of the blood that enters the pulmonary circulation. Full bypass is almost always required in neonates and small infants.

Over the years, the sophisticated CPB system has been modified and miniaturized to make it suitable for use in the smallest of infants and to minimize morbidity [253, 254]. Many elements are common to all perfusion circuits used for bypass in the neonate (Fig. 11.33). The following sections describe the various components of a CPB circuit:

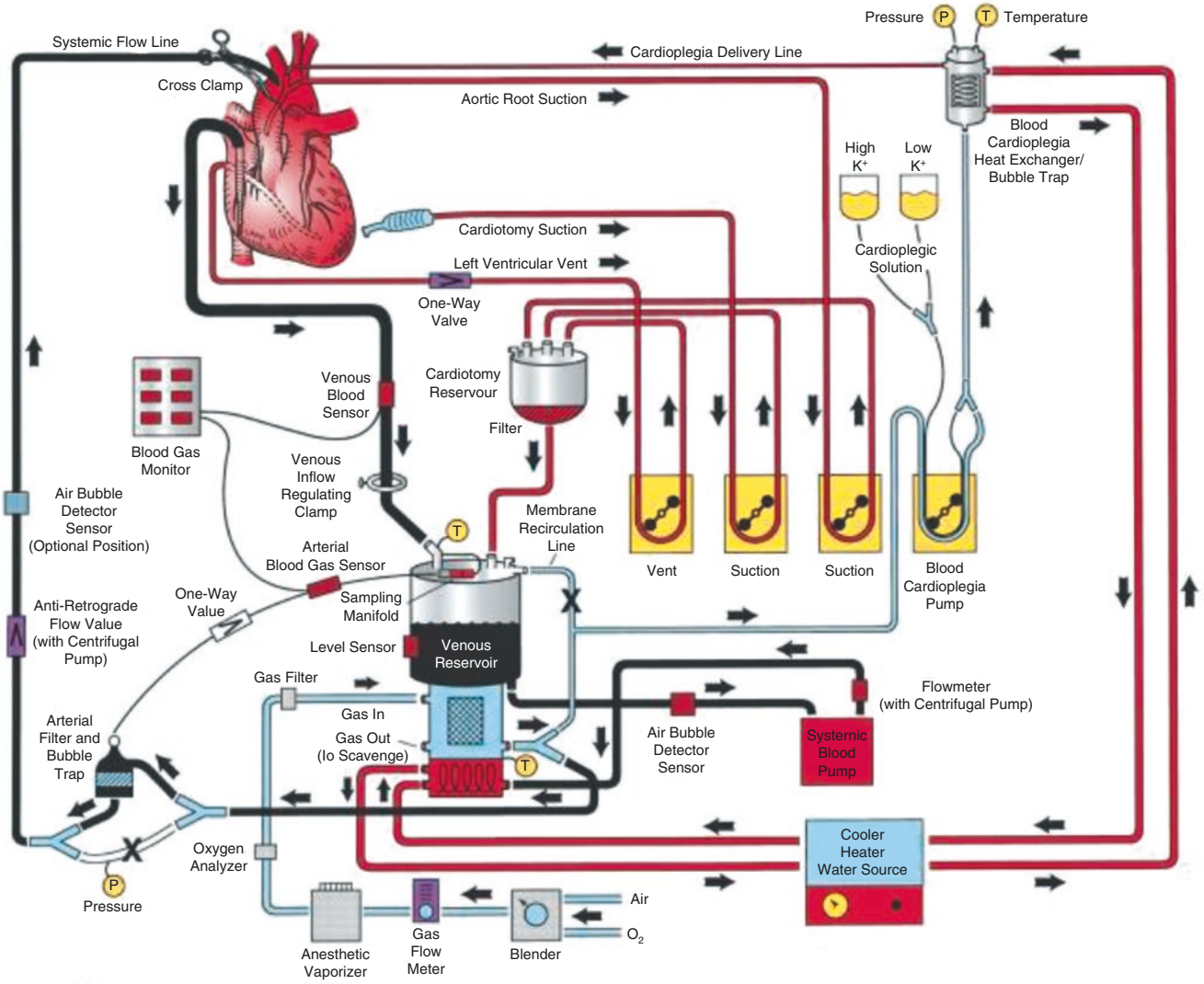

Fig. 11.33 Schematic diagram of a cardiopulmonary bypass circuit. Note the venous reservoir with integrated membrane oxygenator. Other components of the circuit include the cardioplegia solution and pump, water heater/cooler, safety devices, and monitors. The flow is driven by either a roller head or centrifugal pump. Bicaval cannulation may be required during pediatric cardiac surgery for venous drainage, in contrast to a single cannula as depicted here. Carbon dioxide can be added to the inspired gas mixture to facilitate pH-stat blood gas management. Arrows indicate direction of flow, P pressure sensor, T temperature sensors, and X placement of tubing clamps. From Hessel EA II and Shann KG. Blood pumps, circuitry, and cannulation techniques in cardiopulmonary bypass In: Gravlee GP, Davis RF, Hammon JW, and Kussman BD editors. *Cardiopulmonary Bypass and Mechanical Support: Principles and Practice*. 3rd Ed. Philadelphia: Lippincott Williams & Wilkins; 2016; with permission

Heart-Lung Machine [(Pump]

Most are non-pulsatile. Occlusive roller pumps are favored because of their accuracy at very low-flow rates as well as their smooth revolutions at very low speed (revolutions per minute). Most machines incorporate a servo regulating reservoir level sensor, high-pressure alarm, and a bubble detector.

Heat Exchanger Unit

These devices cool and warm the blood. In the neonate, an important feature of these units is their ability to change temperatures very slowly and precisely, thereby providing for adequate equilibration of temperature between blood and tissues, during both cooling and warming.

Membrane Oxygenator

This unit enables gas exchange. The optimal device should be efficient, require a small priming volume, provide appropriate flow capabilities, and be dependable. In addition to heparizing the neonate before CPB to prevent clot formation [255], some manufacturers coat the surface of the CPB circuitry including the oxygenator, to further reduce the prothrombotic risk [256].

Arterial Filter

Various arterial filters are available to preclude particulate matter from entering the arterial return line. Desirable features include a low priming volume, suitable flow capabilities, and ease of debubbling. A coating, as described for the membrane oxygenator, provides similar benefits.

Cannulas and Tubing

The selection of cannulas and tubing is based primarily on the flow requirements. Selecting cannulas of appropriate size is extremely important for proper arterial flow and venous drainage in pediatric patients. The size of the neonate/anatomic structures (systemic veins, RA, Ao) influences the selection of bypass cannulas. Drainage of venous return can be accomplished in some cases by a single RA cannula, although frequently the need for intracardiac surgery requires bicaval cannulation as an alternative to circulatory arrest. Abnormal venous anatomy may require the use of additional cannulas. The arterial cannula, which returns blood to the neonate, typically is placed in the Asc Ao. However, depending on the bypass strategy, this site might be altered to a more distal location. Also based on the nature of the intervention, additional arterial cannula sites may be considered to ensure ACP (graft in innominate artery) or to maintain distal systemic blood flow (e.g., ductal cannulation).

Venous Reservoir

The reservoir functions as the temporary storage site for venous blood during extracorporeal circulatory support. Venous drainage generally is passive, relying on gravity. Vacuum-assisted venous drainage can be an option to facilitate the egress of blood from the patient into the venous reservoir; however, this procedure can traumatize blood elements.

Air/Oxygen Blender, Carbon Dioxide Tank, High–/Low-Flow Meter

These instruments provide capabilities for controlling pO_2 and pCO_2 precisely at all temperatures, facilitating blood gas management on bypass.

Cardioplegia Circuit

This circuit is designed to deliver cardioplegic solution and frequently incorporates the ability for cooling.

Blood Hemoconcentrator

This unit allows for ultrafiltration to be performed during CPB aimed at removing free water and inflammatory mediators.

Venous Saturation and Hematocrit Monitor

These monitors, once appropriately calibrated, serve to enhance the overall safety of the CPB process and allow for less frequent blood sampling.

Activated Clotting Time Machine

This machine is able to provide point-of-care testing of the heparin activity that is monitored by measuring the activated clotting time (ACT) and facilitates anticoagulation management. Various agents can be used as activators of the coagulation system. Kaolin is favored because it is much less influenced by antifibrinolytic agents.

Arterial Blood Gas Machine

Sampling of gas exchange, acid-base status, hematocrit, and other chemistries is mandatory during CPB. Having immediate accessibility to equipment with those capabilities is essential during cases that require bypass.

Cell Saver

This system is used to process the sequestered blood aspirated from the operative field, allowing it to be reinfused with the goal of decreasing exposure to homologous blood products (in some cases).

Miniaturization of Bypass Circuit

The miniaturized bypass apparatus provides a simple and safe method to reduce autologous blood transfusions in the neonate. The small components can significantly decrease priming volumes, thus reducing the enormous disproportion between the extracorporeal volume and small blood volume of the neonate. A small prime volume circuit consisting of only a rotary blood pump head and a membrane oxygenator is used. The venous blood returns to the pump through active drainage. No venous reservoir or cardiotomy suction device is used, minimizing hemodilution and mechanical blood trauma but at the expense of safety features. Recent studies

demonstrate that a miniaturized circuit significantly reduced blood transfusions although the short-term outcomes were similar [257].

Pump Prime

During the pre-bypass period, the pump prime is adjusted to a physiologically balanced solution, with a desirable hematocrit, procoagulant levels, and oncotic pressure. Other additives may include antibiotics, antifibrinolytic agents, and corticosteroids.

Stages of Cardiopulmonary Bypass

Before CPB, the patient's blood is anticoagulated, purse-string sutures are placed, and arterial and venous sites are cannulated. After CPB initiation the following occurs in sequence: core cooling, Ao clamping and myocardial protection, the surgical intervention, followed by warming, release of the Ao clamp, reperfusion of the heart, separation from support, reversal of anticoagulation, and removal of the cannulas. The following sections highlight selected aspects of the bypass period.

Anticoagulation

Before placing the cannulas for CPB, heparin is administered, and appropriate anticoagulation should be confirmed. Neonates have greater water content and volume of distribution for hydrophilic drugs such as heparin compared with older children. The hemostatic system is immature at birth with reduced levels of thrombin, prothrombin, and antithrombin. Most neonates require relatively large doses of heparin [~400 units/kg] due to a relative heparin "resistance" to achieve a target ACT as compared with older children [258]. The optimal ACT for CPB is controversial, but most centers consider a value in excess of 400 s to be the minimum value to proceed to CPB (480 s at some institutions). A subtherapeutic ACT can result from inadequate dosing, low concentrations of antithrombin III, or relative heparin "resistance." One alternative to ACT testing is to measure the heparin concentration [259, 260]. Heparin is also added to the bypass circuit prior to initiation of CPB and at regular intervals thereafter, with serial monitoring of the ACT. Conditions such as hypothermia and renal dysfunction delay the elimination of heparin.

Cannulation and Initiation of Cardiopulmonary Bypass

Transient decreases in blood pressure, mild arterial desaturation, and transient arrhythmias frequently occur when purse strings and cannulae are placed in the neonate. These changes are expected, and usually no treatment or only a minor intervention, such as volume replacement, is required. Any blood lost into venous cannulas during their insertion and priming the circuit should be immediately replaced via the arterial cannula. The goal is to avoid any immediate pre-bypass significant hemodynamic instability or cardiac compromise. Before CPB, satisfactory position of the arterial cannula can be assessed by comparing the mean arterial pressures from the arterial line with that of the arterial inflow cannula of the bypass circuit to the patient.

Once CPB is established, the adequacy of venous drainage should be confirmed. This can be achieved among several ways by direct inspection of the heart, confirmation of a low CVP measurement, and assessment of NIRS values. In addition, venous distension of head structures (e.g., bulging fontanelles, facial congestion), which could suggest SVC obstruction, should be excluded. Be aware that even modest increases in SVC pressure can compromise cerebral blood flow during CPB. Despite priming the bypass circuit with banked blood in the neonate, low arterial pressures related to hemodilution are sometimes seen upon initiation of CPB, especially in infants with cyanotic lesions. In most cases, this situation is associated with a transient decrease in rSO_2 as documented by NIRS monitoring. Increasing pump flows for a brief period of time or early surgical control of runoff connections (i.e., ductus arteriosus, aortopulmonary collaterals, shunts) frequently restores perfusion pressures to acceptable levels. The use of vasoconstricting agents is undesirable as an important goal at this stage is the homogeneous cooling of systemic vascular beds.

The adequacy of perfusion should be assessed carefully throughout the entire period of extracorporeal support. This assessment is based on the pump flow rate, mean arterial pressure on bypass, and measurements of mixed venous saturation. Additional indirect indices include arterial blood gas analysis (pH, lactate, base deficit), regional oxygenation measurements by NIRS, and urine output.

Maintaining adequate anesthesia during CPB is important; light anesthesia, particularly during the cooling or warming phases of the procedure, can lead to a significant increase in metabolic rate and oxygen consumption, with an increase in systemic vascular tone, compromising organ perfusion.

Cooling and Temperature Management

Active cooling using the CPB circuit is initiated once it is confirmed that bypass is satisfactorily established. The goal of hypothermia during CPB is to decrease the metabolic rate, thereby preserving vital organ function [261]. Three levels of hypothermia are used based on the nature of the intervention: mild (30–36 °C), moderate (22–30 °C), and deep hypothermia (18–22 °C). Extensive or complex surgery that requires low-flow perfusion or circulatory arrest is more likely performed under moderate or deep hypothermia. Surface cooling of the brain by applying ice bags to the neonatal head is still used in clinical practice, particularly during conditions of low-flow or circulatory arrest. A key objective of cooling is to uniformly reduce the temperature of all body tissues homogenously, that is, without local temperature gradients. Vasodilators (phentolamine, phenoxybenzamine, nitroprusside) are used during the initial phase of cooling to accomplish this goal, particularly when deep

hypothermia is planned [262–264]. Slow cooling is favored over rapid cooling, as the latter has been linked to neurologic impairment [265]. Although most neonatal surgeries are performed under hypothermic conditions, some centers advocate for normothermia [266, 267]. Ongoing debate on this topic continues [268, 269].

Aortic Cross-Clamping and Myocardial Protection

If myocardial arrest is planned, Ao clamping is performed in order to deliver a cardioplegic solution into the Ao root or, in some cases, directly into the coronary arteries. The goal of cardioplegia is to preserve the myocardium while the heart is ischemic. The Ao clamp usually is placed between the arterial cannula and Ao root. The catheter used to deliver cardioplegia into the root in antegrade fashion typically is placed just below the Ao clamp. A number of cardioplegic solutions are used in clinical practice. The optimal combination of ingredients in these solutions is the subject of ongoing debate. The advantages of blood cardioplegic solutions have led to its increasing use in neonatal patients. After the initial infusion of cardioplegia, additional doses can be given at regular intervals, as needed, depending on the duration of the ischemic time. A good general guide for the perfusionist is to deliver cardioplegic solution at a pressure near the diastolic blood pressure of each individual patient before bypass. This delivery usually is coupled with surface cooling of the heart for added myocardial protection. A venting catheter (vent) is placed in the LV to decompress it. The distribution of cardioplegic solutions throughout the infant myocardium may be compromised by hypertrophy and abnormal coronary artery distribution or other pathology.

Release of Aortic Clamp and Myocardial Reperfusion

Once all extraneous air has been removed from the heart, the Ao clamp is released, allowing for reperfusion of the myocardium, initiation of electrical activity, and spontaneous cardiac beating soon thereafter. TEE can be useful to assist in removing any remaining intracardiac air at this stage. In some cases, cardioversion/defibrillation and/or pacing is required during this phase of CPB. Warming is initiated around this time as a gradual, slow process. Several temperature targets have been proposed and vary according to monitoring site (nasopharyngeal end point > 35 °C, skin > 30 °C, bladder > 35 °C, rectal > 35.5 °C) [270, 271]. The temperature of the perfusate should not exceed 37 °C, as cerebral hyperthermia at this stage can be very detrimental to the neonatal brain [272]. In fact, a mild degree of hypothermia is more desirable.

Separation from CPB, Reversal of Anticoagulation, and Removal of Cannulas

After the Ao clamp has been removed, active rewarming begins and vasoactive/inotropic infusions are initiated as needed. The preference for vasoactive/inotropic agents varies among institutions [273]. Some centers favor dopamine as the first-line inotrope, whereas others favor epinephrine and yet others favor dobutamine [274]. Importantly all these drugs increase heart rate, have arrhythmogenic potential, and increase oxygen consumption [275]. Vasopressin has been increasingly reported as an agent to enhance systemic vascular tone [276–279]. A study in neonates after the Norwood procedure or arterial switch operation demonstrated that low-dose vasopressin decreased the need for fluid resuscitation and catecholamines during the first postoperative day [280]. Milrinone, with inotropic properties as well as pulmonary and systemic vasodilatory effects, is of benefit after neonatal cardiac surgery [281]. The drug is useful in reducing the risk of a postoperative low cardiac output state and thus is used frequently. During the rewarming phase, supplemental doses of muscle relaxants and sedatives should be considered. Blood components can be added to the circuit during this time in order to optimize hematocrit and coagulation factors. Once the neonate's target temperature has been reached and ventilation established, weaning from CPB may be commenced. This is a critical intraoperative time period. As the myocardium has suffered a major stress, this process takes place slowly over several minutes guided by factors such as the appearance of the heart on direct inspection, TEE monitoring, and hemodynamic parameters (filling pressures, arterial blood pressure). The administration of calcium as an infusion and/or as intermittent boluses is often necessary during separation from CPB in the neonate to address the dependence of the neonatal myocardium on free cytosolic ionized calcium for contractility and in order to offset the effects of citrated blood products on serum ionized calcium levels. If any rhythm other than sinus rhythm is present, pacing wires should be placed and sequential pacing initiated. Once circulatory support has been discontinued and hemodynamics optimized, results of the intervention are evaluated. TEE is of significant benefit in this regard. If the results of the intervention are deemed satisfactory, anticoagulation is antagonized with protamine, cannulas are removed, and efforts towards establishing hemostasis are initiated. If significant hemodynamic residua are identified, a return to bypass may be necessary. In most infants undergoing open-heart interventions, temporary epicardial pacing wires are placed. In addition to being used for pacing as needed, atrial wires facilitate the identification of rhythm disturbances as they allow for an atrial electrogram to be obtained. At the conclusion of the surgical procedure and after the mediastinal drainage tubes are placed, chest is closed. Sternal closure may be delayed if severe cardiac dysfunction requiring significant inotropic support, myocardial edema resulting from extensive/complex surgery, pulmonary impairment, bleeding, sustained arrhythmias, or any other concerns regarding the neonate's clinical status were present.

Transport to the Intensive Care Unit

Although early tracheal extubation has been performed successfully in neonates after major cardiac surgery [132, 282, 283], it remains a rare practice, particularly in view of the underlying pathology, nature of the intervention, and concerns for an untoward event. Therefore, with few exceptions, the trachea in most neonates remains intubated postoperatively, even if only for a few hours. Preparing the neonate for transport from the operating room to the intensive care unit is an important time period. Although it can be a distracting time, continuing surveillance of vital signs and hemodynamics during this process is essential as terminating the surgical stimulation may be associated with undesirable changes in blood pressure. Extreme care must be taken to ensure that monitoring and infusion lines are safeguarded during transfer from the operating room table. Note that vertical displacement of some infusion pumps may disturb the flow rates. Adequate oxygenation and ventilation, as well as ongoing hemodynamic monitoring, must be ensured during transport. Hypoventilation during this time can negatively affect pulmonary vascular tone and overall clinical status in the fragile neonate. Adequate analgesia and, in most cases, sedation are important postoperative requirements.

A comprehensive report of the intraoperative course should be given to the team involved in the postoperative care (anesthesia handoff). This report should include airway management (ETT size, ease, and depth of tracheal intubation), location of vascular access and invasive monitors, presence/numbers of chest draining tubes, pacing wires, pacemaker settings as appropriate, implanted surgical hardware, duration of bypass, ischemic time, and doses of active infusions of drugs. Highlights of the procedure and problems should be discussed, as should TEE findings and plan, in addition to any specific concerns. Upon arrival in the intensive care unit, a chest radiograph and blood samples are usually obtained, and ideally the anesthesia provider should review these results. The hemodynamic management of the neonate with CHD in the postoperative setting assumes many of the same physiologic principles applicable to intraoperative care.

Special Cardiopulmonary Bypass Techniques: Deep Hypothermic Circulatory Arrest, Selective Antegrade Cerebral Perfusion, and Others

Deep hypothermic circulatory arrest and selective antegrade cerebral perfusion (SACP; also referred to as antegrade cerebral perfusion (ACP), regional low-flow cerebral perfusion (RLFP), or regional cerebral perfusion) are techniques used in association with CPB during neonatal cardiac surgery. Circulatory arrest is commonly used for cardiac interventions involving the atria or aortic arch. These include Ao arch reconstructive procedures such as the Norwood operation and in some cases repair of total anomalous pulmonary venous connection. DHCA involves lower levels of hypothermia (<20 °C) and cessation of bypass flow while the procedure is undertaken. This technique allows for a surgical field free of cannulae and blood, thus facilitating the surgery. Not surprisingly, prolonged duration of DHCA has been associated with increased neurologic morbidity [284]. Hence, alternate modalities such as SACP have been developed to maintain continuous cerebral circulation and to minimize or avoid the need for circulatory arrest and potentially to prevent hypoxic ischemic injury [285–288]. However, the specific technique for SACP varies among centers. In some cases, a cannula is advanced into the Asc Ao to provide flow to the brain, whereas in others, a graft is sewn into the base of the innominate or subclavian artery to position the arterial cannula away from the surgical field (Fig. 11.34) [138]. At the time of SACP and after the nasopharyngeal temperature has reached a target value of ~ 18 to 20 °C or the rectal temperature has reached 20 to 22 °C (these temperatures vary among institutions), snares are placed around the aortic arch/arch vessels and pump flow is reduced to approximately 30% of the predicted full flow. This approach allows for selective

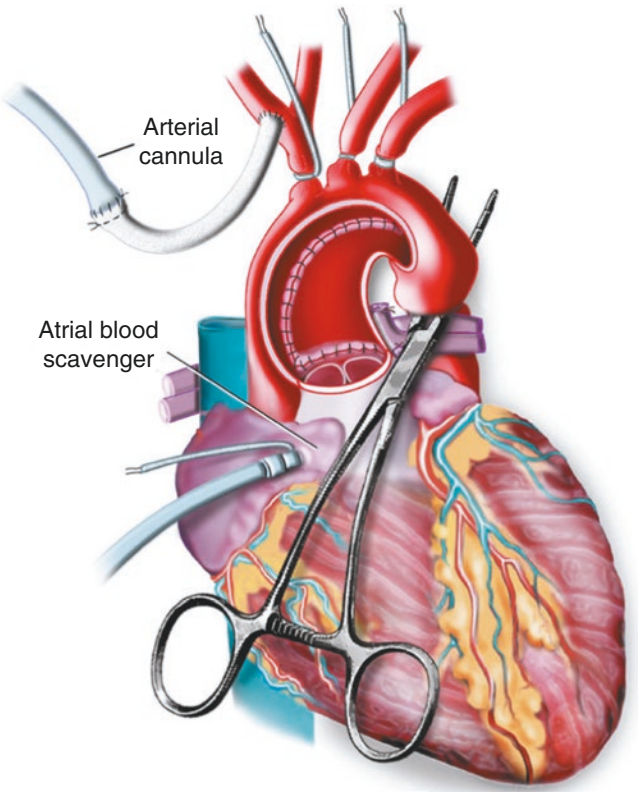

Fig. 11.34 The figure depicts the technique for selective (antegrade) cerebral perfusion. Note the polytetrafluoroethylene graft that has been sewn into the base of the right innominate artery and attached to the arterial inflow cannula of the cardiopulmonary bypass circuit. This allows for flow to the brain and a bloodless operative field while aortic arch reconstruction is undertaken. From Gertler R, Gottlieb EA, Andropoulos DB. Cardiopulmonary Bypass and Management. In: Cote CJ, Lerman J, Anderson B, editors. *A Practice of Anesthesia for Infants and Children*. 6th Ed. Philadelphia: Elsevier; 2019; with permission

blood flow to the brain. The adequacy of brain perfusion during this period is guided by neuromonitoring [137, 236]. After the Ao arch reconstruction is completed, full bypass flow is re-established. A study using magnetic resonance imaging examined the 12-month neurodevelopmental outcomes in neonates undergoing Ao arch reconstruction [289]. They determined that the technique was effective and safe in supporting the brain. Alternate techniques of beating-heart surgery for aortic arch surgery in neonates have also been reported [290, 291].

Unique Aspects of Neonatal Cardiopulmonary Bypass and Differences From the Adult

Notable differences exist between CPB in the neonate and in the adult (Table 11.6). Different techniques are used and the effects of these techniques on the infant's physiology also differ, whereas in all age groups in which hypothermia is used during cardiac surgery, the neonate is more likely to undergo lower levels of hypothermia. Strategies such as total circulatory arrest, low-flow bypass, and SACP are used frequently during complex neonatal surgery. Vasodilating agents such as alpha-blocking drugs are more likely associated with these strategies in the neonate. Flow requirements and perfusion pressures also differ among patients according to age, weight, and body surface area. Recommended flow rates in the neonate (2.6–3.2 L/min/m^2) are greater than in the infant (2.4–2.6 L/min/m^2). During neonatal surgery, a wide range of bypass flow rates are used from no flow during DHCA to large flow rates of 200 mL/kg/min, depending on the particular strategy. The need for variable flow rates is less likely in older children or adults. Perfusion pressures are usually lower in the neonate (~35–40 mmHg), because of the reduced impedance in the systemic circulation.

Blood gas management during hypothermic bypass in the neonate has been controversial in the past. The pH-stat acid-based strategy is used more frequently in the neonate/child, in contrast to the alpha-stat strategy in the adult. The pH-stat acid-base approach maintains a constant blood pH at all temperatures; in other words, pH management is temperature-corrected and targets a $PaCO_2$ of 40 and pH of 7.40 at the patient's actual temperature. Oftentimes, carbon dioxide is introduced into the oxygenator in order to maintain these parameters within a desirable range during hypothermic CPB. The proposed benefits of the temperature-corrected pH-stat approach in pediatric patients favor tissue oxygenation and cerebral vasodilation, thereby allowing for more uniform cooling and better brain protection [292]. The pH-stat approach yields better outcomes with shorter ventilation times and intensive care unit stays [293]. In contrast, the alpha-stat approach corrects the blood gas results to 37 °C irrespective of the child's actual body temperature. In other words, alpha-stat maintains the uncorrected $PaCO_2$ and pH values at normal levels.

Cannulation for CPB in the pediatric age group frequently differs from that in the adult. In the young, placing cannulas in both caval veins (bicaval cannulation) sequesters all the venous return and facilitates intracardiac interventions. In contrast, this procedure is rarely necessary in the adult. In some cases, even additional venous cannulas are required in congenital surgery due to abnormal systemic venous anatomy. The site of arterial cannulation also may vary in pediatric versus adult patients. In fact, during neonatal cardiac surgery, multiple sites of arterial cannulation (e.g., Asc Ao and ductus arteriosus during repair of IAA) may be required. The use of ultrafiltration is standard in the neonate but is rarely used in adults [294]. Conventional

Table 11.6 Differences between pediatric and adult cardiopulmonary bypass

Parameter	Pediatric	Adult
Temperature	Commonly 18–20 °C	Rarely below 32 °C
Use of deep hypothermic circulatory arrest	Common	Rare
Pump prime components	Blood products and albumin	Crystalloid solutions
Dilution effect of pump prime	Up to 200%	25–33%
Perfusion pressure	30–50 mmHg	50–80 mmHg
Cannulation sites	Variable (arterial may include ductus arteriosus and main pulmonary artery; venous, mostly bicaval, may require additional cannulas)	Standardized, mostly ascending aorta and single venous cannula
Flow rates	0–250 mL/kg/min	2.5 L/min/m^2 or 50–65 mL/kg/min
Blood gas management	pH-stat favored	Alpha-stat preferred
Hypoglycemia	Common, due to low hepatic glycogen stores	Rare, seen with severe hepatic dysfunction
Hyperglycemia	Less common	Frequent, increases mortality
Cannulation techniques	Variable, including ductus, aorta, main pulmonary artery, mostly bicaval venous cannulation	Standardized, mostly ascending and single-stage venous cannula
Ultrafiltration	Standard modified ultrafiltration or conventional ultrafiltration	Rare

Modified from Gertler R, Andropoulos DB, and Resheidat A. Cardiopulmonary bypass. In Andropoulos DB, Mossad EB, and Gottlieb EA editors. Anesthesia for Congenital Heart Disease, fourth Ed, Hoboken: Wiley-Blackwell; 2023; with permission

ultrafiltration (CUF) during bypass or modified ultrafiltration (MUF) at the completion of bypass removes body water, increases hematocrit, and reduces the plasma concentration of circulating cytokines and vasoactive substances [295]. This decreases blood transfusion requirements, improves coagulation status, and confers additional significant benefits involving major organ function [296]. A meta-analysis demonstrated that MUF after pediatric cardiac surgery significantly increased the hematocrit and mean arterial pressure after CPB as compared with CUF. However, postoperative outcome parameters including chest tube drainage, ventilator time, and duration of intensive care unit stay remained unchanged [297].

Many physiologic effects of CPB differ between children and adults. In neonates there is a larger disproportion of the pump prime volume relative to the patient's blood volume. Thus, there is the need for whole blood or packed red cells and plasma in the prime to achieve a target hematocrit and thus ensure adequate oxygen carrying capacity. In the past, the target during hypothermic CPB was a low hematocrit, but over time, the target has increased from 20% to 30% as evidence has demonstrated better short-term outcomes and 1-year neurodevelopmental scores with a higher hematocrit [298]. However, a follow-up study that compared hematocrit levels of 25% and 35% showed no major benefits or risks of the greater hematocrit among infants undergoing two-ventricle surgery [299].

Glucose homeostasis is important in neonates undergoing cardiac surgery. Although the neonate is prone to hypoglycemia, there is a tendency towards hyperglycemia during periods of stress. Both of these glucose perturbations have been associated with adverse clinical outcomes. The reduced hepatic glycogen stores, particularly during physiologic stress, increase the risk for hypoglycemia in the neonate, which supports the routine use of glucose-containing intravenous solutions to prevent related morbidity in this population. However, CPB can lead to hyperglycemia by activating the stress response, through the use of components that contain large amounts of glucose (e.g., blood products and cardioplegic solution) and the administration of steroids.

The perioperative management of glucose during pediatric cardiac surgery remains a controversial issue, largely the result of limited and conflicting data [300, 301]. Some studies reported a link between hyperglycemia and poor outcomes after cardiac surgery in children [302, 303]. Postoperative hyperglycemia upon arrival at the intensive care unit has been associated with a younger patient age, reduced body weight, and decreased bypass temperature [304]. Conversely, an investigation using tight glycemic control with the use of insulin in children (similar to that shown to be beneficial during adult cardiac surgery) failed to significantly affect the infection rate, mortality, duration of stay, or measures of organ failure after pediatric cardiac surgery, questioning the utility of this strategy [305]. This latter finding is consistent with previous data that suggested that post-bypass and postoperative hyperglycemia were not risk factors associated with increased morbidity and mortality after cardiac surgery in the infant [306].

Effects of Cardiopulmonary Bypass and Related Strategies

Cardiopulmonary bypass, though essential for the correction of many lesions in the neonate, introduces several significant adverse physiological effects. These effects pose major challenges in the postoperative period.

Systemic Inflammatory Response Syndrome

The systemic inflammatory response syndrome (SIRS) is characterized by a capillary leak state, body edema, hemodynamic instability, and multisystem organ dysfunction [307]. Although the mechanisms responsible for the development of this syndrome are not fully understood, it is thought that activation of humoral cascades due to contact of blood components and endothelial cells with the plastic circuit surfaces plays a major role [308, 309]. Other systems activated during CPB include the complement system, coagulation, and fibrinolytic cascades. SIRS has been linked to major morbidity and mortality rates in the pediatric age group [310, 311]. Several bypass strategies have been devised to ameliorate the inflammatory response and its associated morbidity including heparin coating of circuits, ultrafiltration, the administration of corticosteroids, the use of protease inhibitors (such as aprotinin), and other pharmacologic approaches (complement inhibitors, thromboxane antagonists, anticytokine therapy) [312–315]. Regarding the use of corticosteroids, a recent randomized controlled trial examined the impact of intraoperative methylprednisolone in the postoperative recovery in neonates undergoing cardiac surgery and failed to demonstrate an overall significant benefit [316]. A recently published prospective, randomized, placebo controlled trial involving infants undergoing cardiac surgery with CPB reported that methylprednisolone did not significantly influence the likelihood of a poor clinical outcome and it was associate with postoperative hyperglycemia requiring appropriate therapy [471].

Effects on Bleeding and Coagulation

Bleeding is a major clinical problem after cardiac surgery in the neonate. Risk factors include low birth weight, use of profound hypothermia, an increased preoperative hematocrit, cyanosis, and complex surgery [317]. The increased risk of bleeding in the neonate is due to immaturity of the coagulation system, characterized by reduced plasma concentrations of both procoagulant and anticoagulant proteins (30–70% of adult values) [318]. The levels of factors II (prothrombin), V, VII, X, XI, XII, and XIII are decreased in the neonate and infant until approximately 6 months of age. The

levels of fibrinogen or dysfunctional fibrinogen are also reduced in neonates [319]. All of these factors are compounded by the relatively large volume of the pump prime relative to the blood volume and the resultant dilutional effect on the coagulation factors. The fact that the liver is not completely functional at birth, given that hepatic maturation continues throughout the first few weeks of life, also compounds the problem. Hypoperfusion states can delay the timing of hepatic maturation, adding further to the bleeding risk.

Many neonatal surgical procedures are complex, requiring extensive surgical dissection, extracardiac suture lines, prolonged periods of CPB, and low levels of hypothermia. Cyanotic CHD is associated with hemostatic abnormalities that include polycythemia, thrombocytopenia, platelet functional abnormalities, disseminated intravascular coagulation, decreased production of coagulation factors (due to impaired liver function and vitamin K deficiency), and fibrinolysis [319]. When these factors are combined with dilutional coagulopathy and platelet dysfunction related to CPB, the risk of bleeding increases.

The need for large volumes of blood and blood components has been associated with poor outcomes. The detrimental effects of blood transfusion include activation of the inflammatory cascade, hemodynamic alterations requiring infusion of vasoactive agents, prolonged duration of mechanical ventilation, and extended duration of intensive care stay and hospitalization [320–323]. Therefore, early detection and treatment of bypass-related coagulopathy, as well as sound transfusion strategies, are essential [324].

An individualized strategy that includes patient-specific heparin and protamine management to optimize anticoagulation and minimize bleeding problems in infants has been advocated [325]. For many years, the approach to bleeding during neonatal cardiac surgery was to administer blood components early and prophylactically. Today, several technologies are available to objectively manage coagulation/bleeding metrics. These point-of-care testing devices provide immediate or rapid results for partial thromboplastin time and prothrombin time, thromboelastography (TEG), rotating thromboelastometry (ROTEM, Fig. 11.35), and specific assays of platelet function (Sonoclot analyzer, PFA-100, and multiplate platelet aggregometer) [326–329]. TEG is a widely available technology that allows for a live graphic display of the coagulation process. This can detect residual anticoagulant or deficiency of clotting factors, poor clot strength, or fibrinolysis. This technology is used now to assess post-bypass coagulopathies and to guide blood component therapy [330–332].

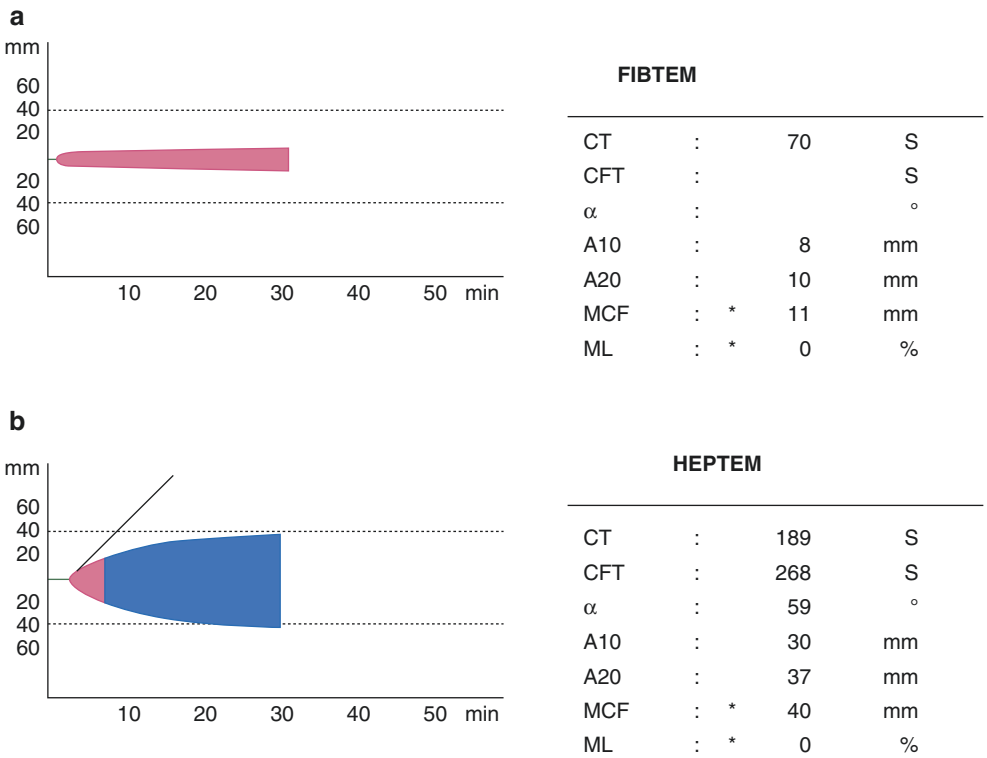

Fig. 11.35 Rotational thromboelastometry (ROTEM) tracing upon rewarming during cardiopulmonary bypass in a neonate undergoing cardiac surgery. **Panel a**, FIBTEM channel showing a borderline MCF value, suggesting inadequate fibrin contribution to clot firmness consistent with a requirement for fibrinogen replacement. **Panel b**, HEPTEM channel displaying prolonged CT and CFT, as well as decreased α angle (<70°) and MCF (<50 mm). This pattern indicates a complex coagulation issue, suggesting the need for clotting factors (plasma or prothrombin complex concentrate) to correct the delay in clot formation (prolonged CT and CFT) and platelets to improve the clot strength (decreased MCF). *CT* coagulation time (seconds), *CFT* clot formation time (seconds), *A10 and A20* amplitude at 10 and 20 min after CT respectively (mm), *ML* maximum lysis (percentage of lysis at any time), *MCF* maximum clot firmness (mm)

Antifibrinolytic agents have been used to minimize bleeding in the perioperative period [333–337]. Agents such as ε-aminocaproic acid (EACA) and tranexamic acid are analogs of the amino acid lysine and exert their antifibrinolytic effects by interfering with the binding of plasminogen to fibrin, which is necessary for activation to plasmin. Recent allometric studies of EACA showed that clearance is reduced in neonates undergoing elective cardiac surgery compared with older children and adults. Dosing should be approximately half that used in children and adults. The current recommendation is a 40 mg/kg loading dose and a 30 mg/kg/h infusion and a loading dose in the bypass prime is of 0.1 mg EACA per 1 mL of blood prime to maintain a target concentration [337]. A pharmacokinetic study of tranexamic acid in neonates and young infants undergoing cardiac surgery proposed dosing recommendations based on selected plasma concentrations [338]. For neonates and infants up to 2 months of age, these ranged between loading doses of 15–120 mg/kg, infusion rates of 2.5–17 mg/kg/h, and CPB prime doses of 20–150 mcg per mL of volume, to maintain target plasma concentrations between 20 μg/mL at the low end and 150 μg/mL at the high end throughout the surgery.

Aprotinin causes inhibition of kallikrein and plasmin. In addition to having hemostatic properties (decreased hemostatic activation, antifibrinolysis, and preservation of platelet adhesiveness), the drug also has favorable effects on inflammation [339]. Based on the published evidence, all three antifibrinolytic agents decrease bleeding to a similar degree [340–343]. However, there are studies that suggest aprotinin is ineffective in neonates undergoing open-heart surgery [344]. Aprotinin was withdrawn from the USA market in 2008 due to the risk of renal dysfunction and death in adult cardiac surgery [345]. These detrimental effects have not been reported in children. Retrospective studies in neonates with renal dysfunction who received aprotinin when the drug was available in the USA indicated that either the duration of CPB or the transfusion of blood products was more likely the etiology for the kidney injury than the drug itself [336, 346, 347].

Despite advances, empiric treatment of excessive bleeding after reversal of heparin may sometimes be needed in the absence of point-of-care testing devices; waiting for the results of coagulation studies can only delay in treatment and additional bleeding. In many cases, components such as platelets, plasma, and cryoprecipitate or human fibrinogen concentrate are still used based on clinical judgment. Products such as activated factor VII (factor VIIa) and prothrombin complex concentrates can be administered in selected cases to manage perioperative surgical coagulopathic bleeding [348, 349]. The use of these products however has raised concerns of their potential prothrombotic risk [350–352].

Neurologic Effects

Neurologic (CNS) morbidity has received increasing attention as survival after neonatal cardiac surgery continues to improve [212, 286, 353–355]. Injury (to the central nervous system during surgery for CHD) can be manifested acutely in the postoperative period as seizures, stroke, and/or coma [286, 356]. The incidence of seizures, as documented by electroencephalographic monitoring, is 14–20% when DHCA or low flow is used but is noted to be infrequent when normal flow rates are used [286, 357]. Seizures are more likely to occur after prolonged duration of DHCA. However, seizures after surgery did not predict worse developmental outcome on short-term follow-up (e.g., after 1 year) of 178 neonates and infants with complex congenital heart defects [358]. With regard to stroke, a study of 122 infants undergoing cardiac surgery reported a prevalence of 10%, half of which was found to exist preoperatively [359]. Most strokes were clinically silent and undetected without neuroimaging. Significant factors associated with stroke identified in multivariate analysis were reduced birth weight, preoperative intubation, reduced intraoperative hematocrit, and greater blood pressure postoperatively at admission to the intensive care unit.

A significant concern is the substantial incidence [>50%] of periventricular leukomalacia reported in neonates after cardiac surgery [360, 361]. This finding of cerebral white matter necrosis that results from injury to immature neurons has been linked to an increased incidence of developmental delay and attention-deficit/hyperactivity disorder [362]. Neurodevelopmental deficiencies after cardiac surgery include problems such as cognitive impairment, speech and language abnormalities, impaired visual and spatial motor skills, impaired attention and executive function, and learning disabilities [363]. There has been intense interest in and investigation of this complication, given the relatively high incidence of neurodevelopmental sequelae among children with CHD [212, 364, 365] . Thus far, patient-specific factors play a significant role on neurologic outcomes [366] as well as potentially modifiable perioperative interventions [289, 367, 368].

Techniques such as DHCA and low-flow bypass have been considered major contributors to these sequelae [286, 369]. In addition, other factors associated with CPB, such as the rate of cooling and rewarming, arterial blood gas management strategy (alpha- versus pH-stat), and hematocrit levels during this period, also impact neurologic outcome [292, 298, 299, 370–372]. The neonate with CHD may have an abnormal and, in many cases, immature central nervous system, potentially also increasing the risk of neurologic injury [328, 373–376]. A younger gestational age has been associated with worse neurodevelopmental outcomes after cardiac surgery during infancy [377]. Preoperative structural brain

abnormalities and abnormal cerebral blood flow are present in neonates with severe CHD [378]. These neurologic abnormalities can be exacerbated by a concomitant genetic syndrome or chromosomal abnormality unrelated to the cardiovascular pathology [379].

Fetuses with left-sided obstructive cardiac lesions have abnormal cerebrovascular physiology, the brain being perfused via retrograde flow through the ductus arteriosus with blood that has a less-than-usual oxygen content. This can affect brain development. For example, microcephaly has been associated with a small Asc Ao [380, 381]. In infants with *d*-TGA, preoperative brain injury has been linked to preoperative balloon atrial septostomy [382], although others dispute this association [383, 384]. To confound matters further, there is the debated issue of the effects of anesthesia in the developing brain as previously noted. The issue of neurologic morbidity in this and other lesions is a complex one, with the evidence suggesting that the etiology is likely multifactorial [385]. Recent data that report a declining incidence of postoperative neonatal brain injury in CHD within the context of higher postoperative blood pressures is reassuring as it suggests that modifiable clinical targets may limit perioperative neurologic morbidity in neonates with complex CHD [386].

In addition to the previously discussed neuroprotective strategies, other approaches have been explored in an effort to limit neurologic morbidity after cardiac surgery [387]. These strategies include specific anesthetic regimens (e.g., ketamine, dexmedetomidine), administration of drugs (e.g., erythropoietin, anti-inflammatory agents, free radical scavengers, and neurotrophic factors), preconditioning (hypoxia-ischemia and remote ischemia), and stem cell treatment [388]. This field continues to evolve, with, as yet, no definitive results that would merit a change in clinical practice.

Pulmonary Effects

Lung injury in the neonate after CPB is manifested by impaired pulmonary function characterized by arterial hypoxemia, carbon dioxide retention, and inability to wean from ventilatory support. The insult likely is the result of ischemic-reperfusion injury and the inflammatory process. Preexisting causes or other issues also contribute to postoperative pulmonary dysfunction. Phrenic nerve injury leading to diaphragmatic paralysis should be excluded by ultrasound or other types of screening. Additional factors possibly involved include atelectasis, pulmonary edema, decreased functional residual capacity, altered total lung capacity, ventilation-perfusion mismatch, and increased dead space [389, 390]. Given that pulmonary complications are one of the most frequent contributors of adverse perioperative outcomes, several approaches that may moderate pulmonary dysfunction (e.g., leukocyte-depleted lung reperfusion) have been explored with variable results [391–393].

Myocardial Effects

An element of myocardial dysfunction after cardiac surgery that requires CPB is present in most, if not all, neonates. The mechanisms appear to be related to ischemia-reperfusion and the inflammatory response [394]. These alterations affect the ability of the myocardium not only to contract (systolic function) but also to relax (ventricular compliance or diastolic function). Thus, inotropes and vasoactive drugs are commonly required. The requirement for these may increase in the first few hours postoperatively.

Renal and Gastrointestinal Effects

Several studies reported an 11% to 17% incidence of varying degrees of acute kidney injury (AKI) in children undergoing CPB [395–397]. Major degrees of AKI portend a poor clinical outcome [398]. The vulnerability of the neonate to AKI is well known and is due to loss of autoregulation and ischemia [395, 399]. Over the years, there has been a growing interest to elucidate the risk factors for AKI in infants undergoing CPB. Five factors predict AKI including younger age, weight < 10 kg, myocardial dysfunction, sepsis, and duration of CPB >90 min [396]. Other studies have reported multiple perioperative risk factors (for acute kidney risk or injury, failure, and mortality in children undergoing CPB) [400–402]. The perioperative use of milrinone, particularly in young infants, and furosemide independently predicted poor renal outcomes. In recognition of the risk of AKI, peritoneal dialysis catheters are routinely placed at some centers after separation from CPB. These catheters can be connected in a sterile manner to a bag and passively allowed to drain or can be used for dialysis as needed for removal of fluid or in the event of reduced renal function in the postoperative period [403]. A randomized clinical trial that compared the use of furosemide and peritoneal dialysis concluded that PD should be strongly considered among infants at high risk for postoperative acute kidney injury and fluid overload [404].

Postoperative gastrointestinal complications associated with CPB are relatively rare. They have been mostly attributed to alterations in splanchnic blood flow and have been linked to high mortality rates in adults [405, 406]. Factors such as hemodynamic instability and the use of vasoactive agents are believed to contribute, although the data are limited. In view of ductal dependency in many congenital lesions and the potential for pulmonary steal, it is not unreasonable to consider the presence of this physiology as a potential perioperative risk. CHD is a risk factor for necrotizing enterocolitis in term infants [405, 407].

A study that quantified the serum transaminase levels as a prognostic factor in children after cardiac surgery determined that increases in transaminases occur more frequently than previously reported, more commonly in the setting of right heart failure [408]. Significant increases in transaminases (alanine aminotransferase [ALT] and aspartate amino-

transferase [AST]) and lactate dehydrogenase (LDH) correlated with decreased postoperative survival.

Cardiothoracic Surgery Without Cardiopulmonary Bypass in the Neonate

In some cases, cardiac surgery can be undertaken without CPB. These interventions can be performed through a lateral thoracotomy or median sternotomy incision. The most common palliative operations are PAB and systemic to pulmonary shunt placement. Corrective procedures that are performed through a thoracotomy include PDA ligation (discussed earlier in this chapter), CoA repair, and vascular ring division. More complex operations, either palliative or corrective, may also be undertaken (e.g., unifocalization of aortopulmonary artery collaterals). From an anesthetic standpoint, these cases require many of the same considerations as outlined above for procedures requiring CPB, reliable vascular access and intraoperative monitoring, as well as planning for postoperative care.

Pulmonary Artery Banding

A palliative approach to mechanically limit excess pulmonary blood flow is to apply a PAB (Fig. 11.36). This intervention may be indicated for pulmonary over-circulation in the neonate with single ventricle physiology, for lesions where the anatomy precludes a definitive repair, or when delaying a corrective procedure is beneficial. The goal of the surgery to restrict pulmonary blood flow is to alleviate congestive symptoms and prevent the development of pulmonary hypertension and eventual changes to the pulmonary vasculature. Sometimes, the procedure is performed via a median sternotomy approach. The adequacy of the PAB can be assessed by direct measurement of the distal PA pressure or by estimation of the band gradient by intraoperative echocardiography. A PA pressure between 25% and 30% of systemic values or peak PAB flow velocity near 3.5 m/s (estimated band gradient of ~ 50 mmHg) is considered satisfactory. The systemic SaO_2, PaO_2, and $ETCO_2$ are very helpful in guiding band adjustments. Tightening the band until $ETCO_2$ just begins to decrease and then loosening it slightly may reliably indicate an optimal band. It is advisable during banding to mimic conditions of room air or minimal inspired oxygen supplementation and normocarbia. In most cases, a PAB improves the symptoms and allows for later staged palliation or corrective repair.

Systemic to Pulmonary Artery Shunt Placement

When pulmonary blood flow is inadequate or ductal dependent, a procedure to increase pulmonary blood flow is indicated. Creation of a systemic-to-PA shunt is usually performed by placement of a graft between the innominate or subclavian artery and a branch PA (mB-T shunt; Fig. 11.37). In many

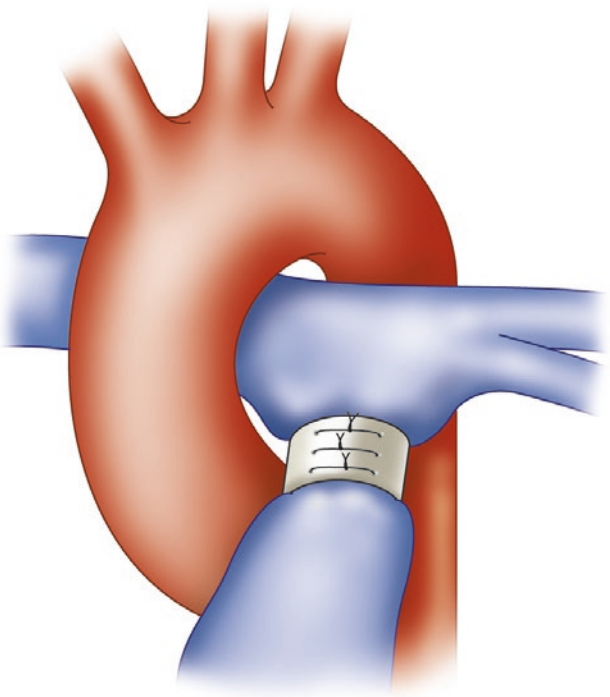

Fig. 11.36 Graphic representation of a pulmonary artery band

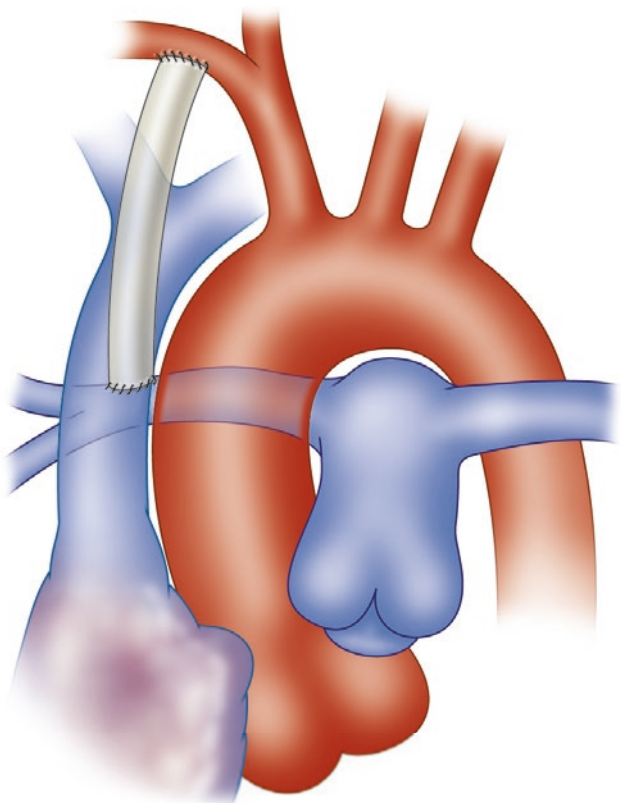

Fig. 11.37 Graphic representation of modified Blalock-Taussig shunt

cases, a central shunt to the MPA may be preferred as this encourages more uniform growth of the branch pulmonary arteries. The surgical approach is by either a median sternotomy or lateral thoracotomy, whereas other extracardiac shunts in most cases require a sternotomy. Specific considerations include the selection of appropriate site(s) for monitoring blood pressure and SpO_2, as this is influenced by the site of the shunt placement, the need to continue PGE_1 infusion intraoperatively, and the administration of low-dose heparin during the intervention. The problems with this procedure are that the partially occluding clamp on the PA will further restrict pulmonary blood flow and that once the anastomosis is commenced, the clamp cannot be removed until the anastomosis is completed. On rare occasions, it may be necessary to administer inotropic agents to support the patient until the clamps can be removed. It is important to ensure adequate oxygenation well before clamp placement. In many instances there may be a need to increase the FiO_2 during shunt placement. Occasionally the position of the clamps needs to be modified to correct significant reductions in pulmonary blood flow. Before and after shunt placement, fluctuations in the level of systemic SaO_2 parallel changes in systemic arterial pressure as it represents the driving force at the Ao end of the ductus arteriosus (preoperatively) or shunt (postoperatively). It is important to confirm the expected changes at the time of shunt unclamping, namely, an increase in SpO_2 and a decrease in diastolic and, possibly, systolic blood pressures, in addition to a widening of the pulse pressure. In rare cases, the decreased diastolic pressure may adversely affect myocardial perfusion leading to ventricular failure; this may require inotrope therapy. After the intervention, if the shunt is too large, an important concern may be successfully balancing the systemic and pulmonary circulations [409]. In some cases the shunt may require banding.

Coarctation of the Aorta Repair

CoA represents one of the most common congenital defects requiring intervention within the first few weeks of life (Fig. 11.38a and b). The surgical approach to this lesion depends on the status of the Ao arch and associated pathology. These factors determine whether the repair is undertaken via a thoracotomy approach, usually as resection of the diseased segment and end-to-end anastomosis (Fig. 11.38c–f) or as a more complex procedure through a median sternotomy incision using CPB. The main considerations for providing care for the neonate during thoracotomy repair include continuation of the PGE_1 infusion (if ongoing), adequate vascular access (may include central venous access depending on clinical status and institutional preference), and ready availability of blood products. A right radial arterial line is preferred for arterial pressure monitoring. The Ao clamp placement may compromise cerebral blood flow and impact rSO_2 as assessed by NIRS; thus, NIRS monitoring has been recommended as a good clinical practice [410]. The need for inotropic support usually is established preoperatively based on the clinical status and echocardiographic assessment of LV systolic function. Continuing the infusion of these drugs perioperatively is appropriate in most cases. Ventilatory adjustments may be required during the dissection phase, as the non-dependent lung is retracted by the surgeon. Significant blood loss is possible [411]. The administration of low-dose heparin (100 units/kg) to obtain a target ACT value near 200 s may be part of the center-specific protocol before applying the Ao cross-clamp. Mild hypothermia [~34–35 °C] is a standard strategy at some centers for spinal cord protection due to the risk of ischemia; however, as previously stated, overt evidence of spinal cord injury in this setting is extremely rare. Transient changes in blood pressure associated with application and removal of the Ao clamp usually are managed by altering the anesthetic depth and augmenting intravascular volume and/or administering calcium. Controlling the blood pressure is a key aspect of postoperative management. Agents such as esmolol, nitroprusside, nicardipine, and others have all been utilized to control post-repair rebound hypertension. Adequate pain control is an important aspect of the perioperative care in these infants. Given the need for perioperative opioid-based analgesia and concomitant risks in the neonate, regional anesthesia techniques have been applied. For thoracotomy options include epidural, intercostal, paravertebral, and newer techniques such as erector spinae blocks [412].

Vascular Ring Division

Vascular rings are anomalies of the great arteries/their branches that can cause extrinsic compression of the tracheobronchial tree and/or esophagus. The presentation usually is that of airway or feeding difficulties. The most common anatomic causes of a vascular ring are a double Ao arch (50–60%) (Fig. 11.39) and a right Ao arch with retroesophageal left subclavian artery and left ligamentum arteriosum (12–25%, Fig. 11.40) [413, 414]. The evaluation of these anomalies frequently requires multimodality imaging [415]. A double Ao usually is an isolated anomaly not associated with CHD. A report indicated that a right-sided Ao arch was dominant in 75% of cases and a left-sided Ao arch in 18%, and arches were of equal size in 7% [416]. Surgical treatment consists of division of the non-dominant arch via thoracotomy. The ligamentum arteriosum or any other constricting bands are also released. Right Ao arch with retroesophageal left subclavian artery and intact ligamentum arteriosum is more likely to be associated with CHD. The approach to this lesion varies, but division of the ligamentum arteriosum is the primary intervention. Passage of an esophageal stethoscope or TEE probe can cause airway obstruction in these patients.

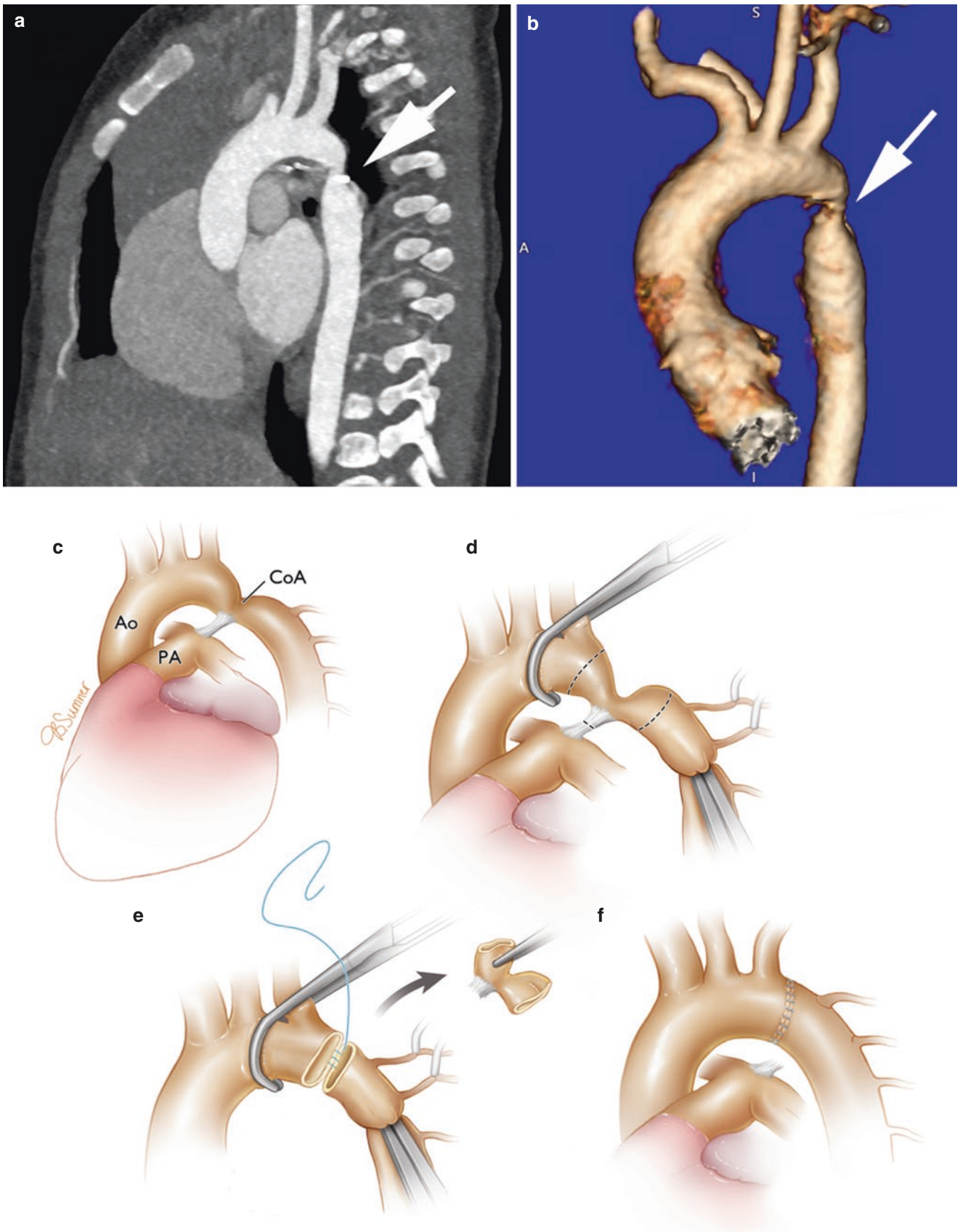

Fig. 11.38 **Panel a**, chest computed tomography showing a discrete aortic coarctation (arrow). **Panel b**, three-dimensional reconstruction in the same neonate showing the region of stenosis immediately beyond the takeoff of an aberrant right subclavian artery. **Panel c**, graphic representation of coarctation of the aorta. **Panels d–f**, illustrations of the surgical technique for coarctation repair including clamp position (**panel d**), resection of diseased segment (**panel e**), and the end-to-end anastomosis (**panel f**). Reproduced with permission from Texas Children's Hospital

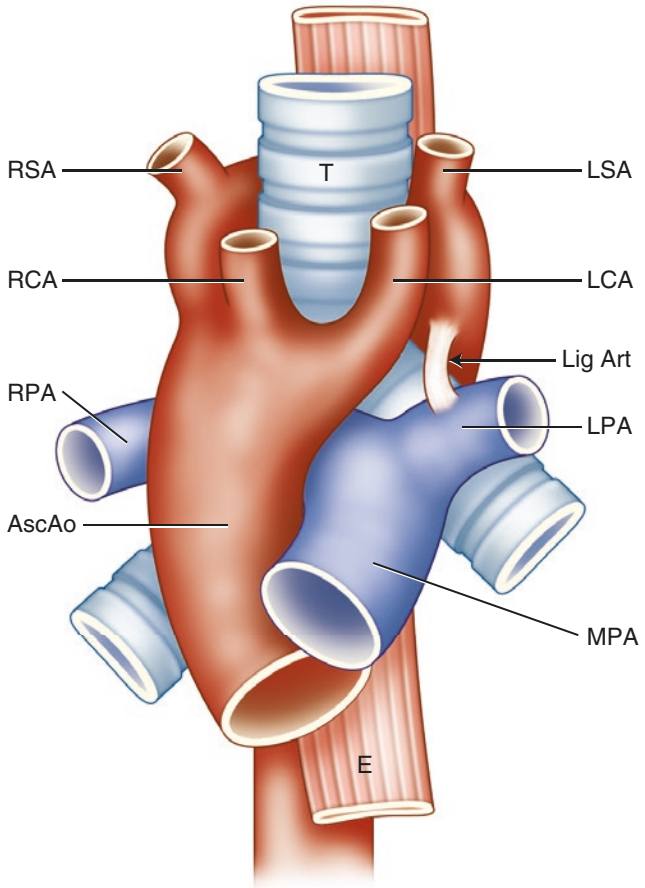

Fig. 11.39 Graphic representation of a double aortic arch. Note the relationship of the right and left aortic arches around the trachea and esophagus. *Asc Ao* ascending aorta, *E* esophagus, *LCA* left carotid artery, *LPA* left pulmonary artery, *LSA* left subclavian artery, *Lig Art* ligamentum arteriosus, *MPA* main pulmonary artery, *RCA* right carotid artery, *RPA* right pulmonary artery, *RSA* right subclavian artery, *T* trachea

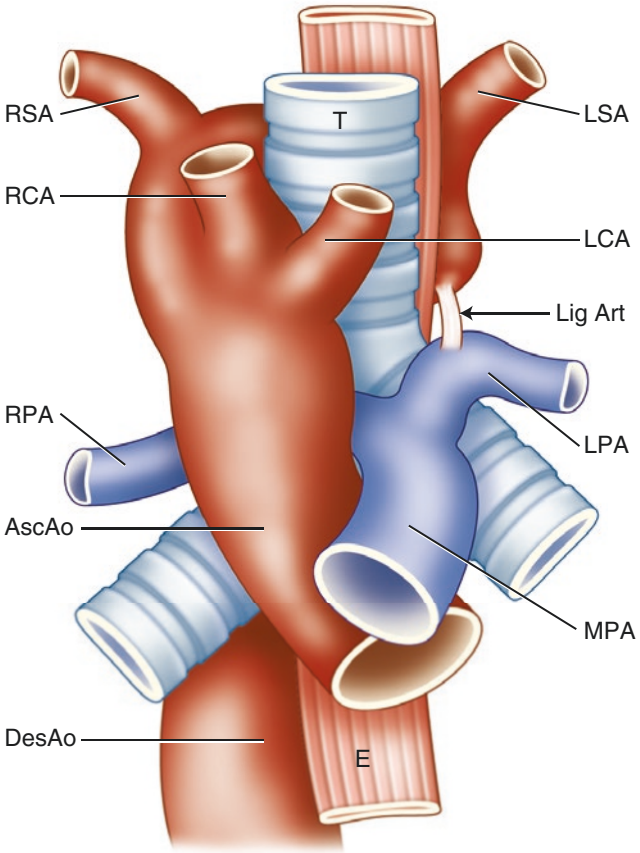

Fig. 11.40 Graphic representation of a right aortic arch and aberrant subclavian artery creating a vascular ring. In this anomaly, a left ductus arteriosus arises from a bulbous region at the base of the left subclavian artery (Kommerell diverticulum) and attaches to the left pulmonary artery. *Asc Ao* ascending aorta, *Des Ao* descending aorta, *E* esophagus, *LCA* left carotid artery, *LPA* left pulmonary artery, *LSA* left subclavian artery, *Lig Art* ligamentum arteriosus, *MPA* main pulmonary artery, *RCA* right carotid artery, *RPA* right pulmonary artery, *RSA* right subclavian artery, *T* trachea

Vascular rings frequently are associated with tracheobronchomalacia and other abnormalities of the airway. Anesthetic care may be required for diagnostic evaluation as well as surgical treatment. In some cases, a formal bronchoscopic examination is performed as part of the overall evaluation. The airway should be assessed during spontaneous ventilation, examining the trachea for pulsatile compression(s). Recognizing that preexisting tracheobronchomalacia persists postoperatively, when it may influence patient management, is also important. Regional anesthesia techniques may be beneficial for postoperative analgesia in these cases.

Mechanical Circulatory Support in the Neonate with Congenital Heart Disease

Circulatory support may be required for cardiac or cardiopulmonary failure [417–420]. The history typically is that of a reversible cause of circulatory failure or a condition that is untreatable/end stage for which the patient awaits heart transplantation. In most cases, there is acute or impending total hemodynamic decompensation. When mechanical support is instituted before circulatory collapse occurs, the goal is to prevent irreversible end-organ damage. Indications for mechanical circulatory support associated with cardiac surgery in the neonate are listed in Table 11.7. This therapy can be applied in the preoperative, intraoperative, or postoperative period. Preoperatively, the indication for support usually is related to either the need for stabilization or due to circulatory compromise. In the intraoperative setting, the use of mechanical support is more likely related to failure to wean from CPB, which may be due to the effects of surgery, bypass, and/or preoperative impairment of myocardial function. This clinical problem is referred to as postcardiotomy failure. More unusual in the intraoperative setting is the unanticipated need for acute circulatory support during procedures that do not require bypass. In the postoperative period, the indication usually is related to a low cardiac out-

Table 11.7 Indications for mechanical circulatory support in the neonate with congenital heart disease

Stabilization prior to cardiac surgery or catheter-based intervention
Inability to wean from cardiopulmonary bypass
Postoperative low cardiac output state
Acute cardiopulmonary decompensation resulting from cardiac surgery

put state or cardiopulmonary arrest. Contraindications to supporting the circulation mechanically include multisystem organ dysfunction, sepsis, severe coagulopathy, neurologic impairment, or intracranial hemorrhage.

Mechanical support in the neonate can be performed using venoarterial ECMO or a ventricular assist device (VAD). These strategies vary somewhat in their abilities to support body functions. ECMO provides isolated support of the respiratory system or full cardiopulmonary support; in contrast, VAD only supports the circulation. The components of an ECMO circuit include a centrifugal or roller pump, hollow fiber membrane oxygenator, oxygen blender, pump console, and heat exchanger. ECMO is the form of mechanical circulatory support used most frequently in the neonate. This choice is due to the extensive clinical experience with the use of ECMO in patients with respiratory failure secondary to meconium aspiration, persistent pulmonary hypertension, and congenital diaphragmatic hernia. ECMO also has been shown to be extremely valuable in the neonate suffering from a cardiopulmonary arrest, serving as rescue therapy [86, 421]. This form of therapy, also referred to as extracorporeal support during cardiopulmonary resuscitation (ECPR) or ECMO during cardiac arrest or rapid response, led to an overall survival of 40% in almost 600 patients who received this therapy [421].

In the less likely case of the neonate with isolated ventricular impairment and good pulmonary function, a VAD may be a better option. In postcardiotomy heart failure, however, numerous considerations come into play. The presence of biventricular dysfunction, hypoxemia, and pulmonary hypertension, common findings in the neonate with CHD, favors the use of ECMO in this patient group. The mortality in pediatric cardiac patients on ECMO remains substantial [422].

When ECMO is required, cannulation is performed either peripherally, using the neck, or centrally, via a sternotomy. Neck access to the central circulation is via the jugular vein and carotid artery. When the sternum is open, cannulas are placed in the RA and Ao, and left-sided ventricular decompression is performed if needed. This is referred to as central cannulation.

There are several different types of VADs that can support the left, right, or both ventricles [423–425]. A biventricular assist device (BIVAD), when necessary, is more likely to be used in the older child. The selection of the form of support depends on many factors, including the nature of the problem, the clinical situation, details of the anatomy (e.g., presence of intracardiac shunts), and pulmonary function. Other issues such as availability of equipment, training of personnel, familiarity among practitioners, and institutional preference also influence the selection of technology. Each support strategy has definitive benefits and limitations, which also have an important impact on decision-making.

VAD is placed via a sternotomy; a temporary centrifugal LVAD, for example, requires an inflow cannula in the LA and an outflow cannula in the Ao. The use of a long-term LVAD in the neonate involves placing an inflow cannula in the LV apex and an outflow cannula in the Asc Ao. At the time of this writing, paracorporeal pulsatile devices, referring to those placed outside the body, are the only option for long-term VAD support in the neonate, in contrast to intracorporeal or implantable devices available in older age groups [426]. The Berlin Heart Excor Pediatric VAD® (Fig. 11.41) was the first device to become commercially available specifically for use in children [427]. This air-driven device is available in a variety of pump sizes including one suitable for the newborn. Already in use in numerous countries for several years, this device was granted regulatory approval in the USA by the Food and Drug Administration for pediatric use as bridge to cardiac transplantation in the USA in 2011 [424, 428]. The device is beneficial to many neonates, infants, and small children [429–431]. The MEDOS HIA® device is also a pneumatic paracorporeal VAD available in Europe for infants and children [432, 433]. It should be emphasized that while all these forms of support are lifesaving and offer the only option for survival in many infants, they are associated with significant morbidity and mortality. Major complications are hemorrhage, thromboembolism, and/or infection [434]. These can result in devastating consequences to the central nervous system. Although good neurological outcomes have been documented after mechanical circulatory support, a number of questions, including long-term neurocognitive outcomes and other important issues that impact quality of life, remain unanswered [435]. Therefore, the deployment of these sophisticated circulatory support

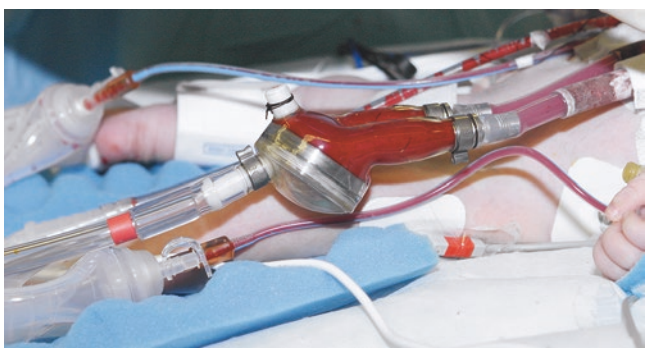

Fig. 11.41 Photograph depicts a Berlin Heart Excor Pediatric VAD® left ventricular assist device in a neonate

modalities requires a careful risk-benefit assessment in recognition of the associated significant potential complications associated with these treatments.

The choice of mechanical support depends on the anticipated duration of therapy (short versus long term). Both ECMO and VAD are suitable support strategies in the short term. This is the case when the goal is used as a bridge to immediate survival, to recovery, to decision-making, or to a prolonged type of support (bridge to bridge). A greater period of circulatory support as a bridge to transplantation requires a different hardware that allows for more patient mobility. Technological innovations over the years have resulted in miniaturization of pumps and cannulas, rendering the use of specialized long-term VAD feasible in the neonate [423, 436, 437].

Anesthetic care of the neonate who requires mechanical support is greatly influenced by factors such as the neonate's clinical condition, situation, and the type of therapy being instituted. During an acute event when ECMO is being applied for immediate survival, management is similar to that involving any cardiopulmonary resuscitation effort in the neonate. Additional considerations include the underlying structural cardiovascular abnormalities, need for anticoagulation, and administration of volume/blood components as needed [438]. Vasodilators are required on occasion upon initiation of support in order to be able to deliver full flows, particularly after vasoconstrictive agents have been administered as part of the resuscitation effort. Although ECMO has been applied on a routine basis in neonates with HLHS after the Norwood procedure to facilitate postoperative management in the past, it is not current practice [439].

The use of short-term circulatory support for postcardiotomy failure usually follows a long operative procedure and several failed attempts at weaning from CPB. An extended bypass period is invariably associated with problems of bleeding, a heightened inflammatory response, potential pulmonary dysfunction, and many other disturbances that complicate management. The need for operative procedures such as mediastinal exploration for bleeding, adjustments of cannula position, or weaning of support requires adequate planning, preparation, and communication among all team members.

Data regarding anesthetic care in children with long-term devices are extremely limited. A study in children with a Berlin Heart, including infants undergoing anesthesia for noncardiac procedures, demonstrated poor tolerance for reductions in systemic vascular resistance due to the relatively fixed cardiac output of the device [440]. Preoperative stability was not predictive of the intraoperative hemodynamic course. The study recommended that volume and alpha-agonists should be used to treat hypotension in this patient group. Lastly, caring for these infants involves greater knowledge than just the technology (e.g., hardware, settings) but also the physiologic aspects of the various circulatory support modalities and anticoagulation algorithms that may be in use [441]. This knowledge implies an understanding of how device parameters can be affected and what types of interventions may be indicated to address any unfavorable hemodynamic effects. For example, an important issue in these patients relates to factors that can influence LV preload and, consequently, filling of the device and stroke volume. Increases in pulmonary vascular tone or acute alterations in RV function can be detrimental. Therefore, strategies that maintain low pulmonary vascular resistance and promote RV performance are essential for successful management of these infants [442].

Perioperative Issues and Some Special Considerations in the Neonate Undergoing Cardiac Surgery

There are special considerations related to individual cardiac defects and the pathophysiology of the disease process, which present challenges in the care of the neonate with heart disease. Some of these potential problems and their intraoperative considerations are addressed briefly below.

Pulmonary Hypertension

Pulmonary hypertension in the neonatal period has different etiologies including persistent pulmonary hypertension of the newborn (PPHN), lung disease such as bronchopulmonary dysplasia, congenital anomalies including congenital diaphragmatic hernia, and CHD. Increased PA pressure is a common feature in congenital cardiovascular diseases. Usually, it results from increased pulmonary blood flow that is caused by an unrestrictive direct communication between the atria, ventricles, and great arteries or an obstruction to pulmonary venous flow [443, 444]. Pulmonary arterial hypertension develops over a variable period depending on the extent to which pulmonary blood flow is increased and the level of the shunt. Lesions associated with excess pulmonary blood flow in the neonatal period or early infancy include a large PDA, VSD, complete atrioventricular septal defect, and over-circulated HLHS. Over time, high-flow lesions can remodel the pulmonary arterial smooth muscle and induce vascular changes. Defects such as TA and AP window predispose to accelerated pulmonary vascular disease. Down syndrome is considered an independent risk factor to develop pulmonary vascular disease [445]. Perioperative management of infants with lesions that predispose to excess pulmonary blood flow includes avoiding

maneuvers that decrease pulmonary vascular resistance so that left-to-right shunting does not increase and exacerbate the increase in pulmonary blood flow. Pulmonary venous hypertension associated with pulmonary venous obstruction, LV failure, or left heart lesions that impede blood flow results in reflex pulmonary arterial hypertension. It can be secondary to defects such as TAPVR, mitral stenosis, cor triatriatum, congenital pulmonary vein stenosis, and HLHS with a restrictive atrial septum. Over time and depending on the degree of obstruction, the lungs become congested and pulmonary arterial hypertension develops. The benefits of early interventions in CHD are limitation of pulmonary blood flow and repair of obstruction to pulmonary venous blood flow. The end result is a reduction in PA pressures and in the likelihood of pulmonary vascular reactivity [446]. Reduced PA pressures and a low vascular resistance are critically relevant in the infant with a single ventricle, as they are prerequisites for future palliative strategies that rely on passive pulmonary blood flow.

In the neonate, predisposing factors for a reactive pulmonary vascular bed during the perioperative period include the underlying increased pulmonary vascular tone, effects of CPB, and physiologic consequences of the cardiac pathology. In neonates with increased pulmonary blood flow or obstruction to pulmonary venous return, the potential for pulmonary hypertension immediately after bypass and in the postoperatively setting should be recognized. Pulmonary hypertensive crises result from acute increases in pulmonary vascular tone, triggered by a variety of factors (Table 11.8). Hemodynamic decompensation during these events is due to acute right heart failure, decreased LV preload related to resistance to the egress of blood across the pulmonary bed, and unfavorable leftward shift of the interventricular septum, compromising LV filling and decreasing cardiac output. Prevention and management of these crises include minimal handling, sedation, and measures that favor a low pulmonary vascular resistance [e.g., hyperventilation, hyperoxygenation, and alkalosis] [447]. Treatment focuses on optimizing RV function using inotropic support as necessary [448]. Milrinone also can be quite helpful to decrease pulmonary vascular tone and enhance RV function [449]. The use of selective pulmonary vasodilators such as inhaled nitric oxide may also be indicated [449, 450].

Table 11.8 Factors that can increase pulmonary vascular tone

Hypoxemia
Hypercarbia
Acidemia
Hypothermia
Atelectasis
Transmitted positive airway pressure
Agitation, pain, stimulation, light anesthesia, stress response

Systemic Hypotension

Intraoperative hypotension can be secondary to factors such as hypovolemia (due to fluid restriction, diuretic therapy, or blood loss), the effects of sedatives/anesthetic agents, rhythm abnormalities, ventricular dysfunction, or mechanical influences of the surgical intervention. A helpful management algorithm to determine the cause and initiate appropriate therapy is to consider the contributions of ventricular preload, contractility, afterload, and factors related to the physiology of the defect, to the hemodynamic problem. In addition, the electrocardiogram should be evaluated for evidence of rhythm disturbances or myocardial ischemia. Treatment should focus on the cause and consider whether it represents an unavoidable transient occurrence related to the procedure itself or an event of more concern. If an acute intervention is necessary to increase blood pressure, it can be accomplished by the administration of volume, calcium, a vasoconstrictor, or other pharmacologic agents while definitive therapy is instituted.

Congestive Heart Failure

In the neonate, congestive heart failure is always biventricular, and failure of one ventricle compromises the action of the other. It can be caused by volume overload resulting from a physiologic left-to-right shunt, severe valvar regurgitation, obstructive pathology, and imbalance between the pulmonary and systemic circulations favoring pulmonary blood flow. Heart failure is also present in conditions associated with poor myocardial contractility. Severe heart failure is a known risk factor for perioperative complications in children [451].

Cyanosis

Cyanosis related to CHD is the result of limited pulmonary blood flow and/or intracardiac mixing. Delayed surgery, palliation, or staged correction of CHD is often associated with some degree of cyanosis. In the neonate, the effects of cyanosis may not be as pronounced as in older infants and children with long-standing hypoxemia. Chronic hypoxemia affects all major organ systems and invokes compensatory mechanisms to enhance systemic oxygen delivery. Despite the favorable effects of these adaptive responses, they can also be detrimental due to increased blood viscosity, red cell sludging, and alterations in the coagulation system. Important perioperative considerations in cyanotic infants include the need for adequate preoperative hydration (refer to the section on fasting period) and meticulous care of venous lines in order to avoid the potential risk of paradoxical embolization (discussion to follow).

Ventricular Pressure Overload

Outflow tract obstruction or increased PA pressure/vascular resistance imposes a pressure load on the ventricle, thereby increasing the wall tension. Compensatory hypertrophy leads to reduced ventricular compliance. This condition results in a vulnerability of the myocardial supply-and-demand relationship, reduced tolerance for factors that can alter this fine balance, and the potential increased risk of ischemia. Be aware that in some defects, RV pressure can exceed the systemic values and negatively impact LV function. The negative effect of the RV on the LV is explained by the direct mechanical interaction between the ventricles referred to as ventricular interdependence.

Ventricular Volume Overload

A volume load to the LV is characterized by increased LA pressure, LV end-diastolic volume, and stroke volume. This physiology is associated with LA and LV dilation and cardiomegaly. The dilated ventricle must generate a greater wall tension to achieve the same intra-cavity pressure [Laplace Law]. This may precipitate ventricular failure. In the postoperative neonate, residual valvar regurgitation can be associated with altered loading conditions that, if significant, can cause congestive symptoms and ventricular dysfunction. Neonates with palliated single ventricles can be particularly vulnerable to conditions associated with ventricular volume overload (e.g., systemic-to-PA shunts).

Myocardial Ischemia

Anomalies associated with increased systolic and diastolic wall stress and those with decreased coronary perfusion secondary to low diastolic pressures (e.g., PDA) may cause myocardial ischemia in the neonate. Lesions such as anomalous origin of the left coronary artery from the pulmonary artery (ALCAPA) and large coronary fistula(s) also have a propensity to develop myocardial ischemia. Although the clinical manifestations of these anomalies usually become evident beyond the neonatal period as pulmonary vascular resistance (ALCAPA) or RV pressure (coronary fistula[s] to the RV) decrease, an element of ischemia can be present in the neonate. For the neonate undergoing a surgical intervention for any type of CHD, the negative effects of CPB, Ao cross-clamp, coronary manipulations, and the procedure itself should also be considered as potential etiologies for myocardial ischemia.

Altered Respiratory Mechanics

Many congenital defects associated with increased pulmonary blood flow and vascular pressures increase LA pressure, leading to interstitial pulmonary edema and compressing small airways. These alterations in lung mechanics increase airway resistance and decrease lung compliance [452]. In addition to inadequate palliation or residual shunts and the effects of surgery, such alterations may further exacerbate the already vulnerable respiratory status of the neonate [453].

Systemic Air Embolization

It is essential to appreciate that the presence of shunts or simply a patent foramen ovale introduces the risk of a right-to-left shunt and a paradoxical systemic air embolus in the neonate. The risk is magnified by the increased right-sided pressures or pulmonary vascular resistance associated with CHD. This risk mandates meticulous de-airing of all vascular lines and the use of in-line air filters where possible.

Conduction Disturbances and Arrhythmias

Infants, particularly those with Down syndrome, can develop bradycardia during induction of anesthesia in association with the administration of drugs (e.g., opioids) and at the time of laryngoscopy tracheal intubation or placement of a TEE probe. Usually, bradycardia is self-limited and requires no treatment; however, if it persists, the administration of drugs such as atropine or glycopyrrolate or, less likely, a small dose of epinephrine if the slow heart rate results in hemodynamic instability should be considered. Cardiac arrhythmias are known to occur during placement of central venous catheters. Usually, arrhythmias are transient and require no intervention unless they persist, in which case either pharmacologic treatment or cardioversion/defibrillation is indicated. Because arrhythmias may not be tolerated in the critically ill neonate, caution must be exercised to minimize stimulation of the heart during central catheter placement by limiting the depth the catheter is inserted to the SVC/IVC-RA junction.

Perioperative Stress Response

The typical physiologic response to painful stimuli in normal children consists of an increase in heart rate and blood pressure and a transient decrease in PaO_2. These normal responses however can be detrimental to infants with CHD. Tachycardia abbreviates the diastolic filling time, and hypertension increases ventricular afterload, thereby decreasing stroke volume. These responses reduce the ability of the neonate with CHD to offset the effect of perioperative stresses with an increase in cardiac output.

Several studies have highlighted adrenal insufficiency in neonates after CPB, as well as the role of corticosteroids in

treating it and reducing the prevalence of postsurgical low cardiac output [454, 455]. At the same time, data have shown that reduced levels of cortisol in the immediate postoperative period are not associated with worse outcomes, nor predictive of steroid responsiveness [456].

Although the use of regional anesthesia in the neonate undergoing major surgery is well documented as previously noted, with benefits that include blunting of the stress response and pain control, the application of these techniques during cardiac surgery remains the subject of debate [457–459]. In many cases, the need for postoperative sedation and mechanical ventilation that frequently includes the use of opioids has limited an interest in perioperative regional techniques [460]. A meta-analysis that compared regional and general anesthesia with general anesthesia plus systemic analgesia for children undergoing cardiac surgery concluded that compared with systemic analgesia, regional techniques decreased postoperative pain for up to 24 h postoperatively [461]. However, it was also noted that "currently there is no evidence that regional anesthesia for pediatric cardiac surgery has any impact on major morbidity and mortality." Given the paucity of data regarding increased benefits of regional anesthesia over standard management, and concerns of complications after neuroaxial anesthesia, there continues to be ongoing reluctance to adopt this approach. This perception has persisted despite the lack of reported adverse events or serious complications after regional analgesia, in children with CHD. The use of regional techniques is more common during thoracic surgery [462].

Post-cardiac Transplant Recipients

Heart transplantation may be the only option for survival for some neonates with CHD that is not amenable to palliation or correction [463, 464]. In neonates, this is more likely to occur in the case of severe cardiac dysfunction, high-risk anatomy, or failed surgical intervention [465]. The use of ABO-incompatible donors has increased over time and has abbreviated the waitlist period [466]. Data thus far have been encouraging in terms of rejection and survival rates [467].

The posttransplanted infant has a denervated heart; the lack of external nerve supply implies that the usual autonomic regulatory mechanisms are not operational, increasing the potential for hemodynamic instability. In addition, compensatory responses can be delayed, further augmenting the likelihood for compromise. Critical determinants of cardiac output include an adequate heart rate and blood volume. In the immediate posttransplant period, heart rate is supported by exogenous chronotropes or pacing. Subsequently, circulating endogenous catecholamines drive the heart rate. Regardless of the time interval from transplantation, when caring for these neonates, the following considerations are suggested: (1) have drugs with chronotropic properties immediately available, (2) use agents with a direct action on the myocardium and vasculature, and (3) prepare for emergent cardiac pacing. Several additional considerations are important in the anesthetic care of the transplanted patient [468]. Immunosuppressant agents, which may need to be given during the perioperative period, may have secondary effects on various organ systems (particularly the heart, liver, and kidney) and can interact with muscle relaxants. Other considerations include the potential need for "stress"-dose corticosteroids (a controversial subject), the requirement for strict aseptic techniques, and the adequate preparation of blood products (irradiated, leukocyte reduced, and cytomegalovirus negative/safe).

Summary

The last few decades have witnessed remarkable improvements in outcomes of CHD in the neonate. However, despite advancements in many aspects of clinical care, neonates with congenital cardiac malformations present ongoing challenges. The ability of the anesthesiologist to provide optimal care depends heavily on an understanding of the structural abnormalities, hemodynamic consequences of the defects, available management strategies, and the impact of anesthetic/surgical interventions on the physiology. Optimal management of the neonate with CHD is most likely to be achieved in specialized centers that have a dedicated comprehensive multidisciplinary team and a large volume of surgical cases [469]. The reader is referred to a recent comprehensive publication by the Neonatal Cardiac Care Collaborative in the form of a journal supplement addressing contemporary topics related to neonatal cardiac care. This work represents a multisocietal effort to outline clinical guidelines for the care of neonates requiring congenital heart surgery and further expands on many of the topics highlighted in this chapter [470].

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ECMO for the Neonate

12

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Introduction

Extracorporeal membrane oxygenation (ECMO) or extracorporeal life support (ECLS) has been utilized to support critically ill neonates, children, and adults for more than 45 years [1]. ECLS, which better describes this technology, is a modified prolonged form of cardiopulmonary bypass (CBP) that can be used in the intensive care unit to support patients with severe, but reversible, cardiopulmonary failure who are unresponsive to conventional treatment. ECMO removes carbon dioxide (CO_2) and adds oxygen (O_2) from blood using an artificial lung (the oxygenator) by draining blood from the venous system and returning it using a pump via an artery (venoarterial [VA] ECMO) or a vein (venovenous [VV] ECMO). The first successful neonatal ECMO was performed by Dr. Robert Bartlett in 1975 in which he supported a 1-day-old baby with severe hypoxic respiratory failure secondary to meconium aspiration pneumonitis [2]. Earlier trials with ECMO support demonstrated improved survival in infants with severe, but potentially reversible, respiratory failure [3–6]. According to the July 2020 report of the extracorporeal life support organization (ELSO) registry, more than 133,000 patients had been supported by ECMO, of which more than 43,000 were neonates, with survival rates of 73% in the neonatal respiratory group.

Despite significant improvements in ECMO equipment, monitoring, understanding of pathophysiology, and widespread clinical experience, complication rates remain concerning including bleeding and thrombosis, which carries a greater morbidity and mortality [7].

It is important to recognize that ECMO is a support modality and not a treatment. It provides caregivers the time to perform diagnostic and therapeutic interventions to facilitate organ recovery while providing gas exchange and optimal tissue perfusion. ECMO is a complex, invasive, high-risk, and costly technology; it is restricted to centers where sufficient experience, up-to-date knowledge, trained personnel, and advanced technology for the use of ECMO in neonates are available.

Patient Selection

ECMO is used for term and near-term neonates with severe respiratory and/or cardiac failure secondary to potentially reversible pathology that has failed conventional therapies. Centers differ in their criteria for eligibility for ECMO, but many follow the ELSO guidelines [8]. Table 12.1 lists the indications and contraindications for neonatal ECMO. These neonates present with inadequate tissue oxygen delivery manifested by hemodynamic instability, lactic acidosis, and multiorgan dysfunction.

Many have severe hypoxic respiratory failure manifested by a $PaO_2 < 40$ mmHg and an oxygenation index (OI) exceeding 40 for >4 h, with or without hypercapnia. The most common underlying etiologies are congenital diaphragmatic hernia (CDH), meconium aspiration syndrome (MAS), sepsis, and primary pulmonary hypertension. Persistent pulmonary hypertension whether primary or secondary increases the right ventricular (RV) afterload. resulting in RV systolic and diastolic dysfunction with RV dilation, which in turn leads to RV failure, a leftward shift of the interventricular septum resulting in left ventricular failure, poor cardiac output, and, if prolonged, biventricular heart failure [8–12].

As soon as a decision to institute ECMO has been confirmed, a complete blood count, serum electrolytes, renal and liver function tests, coagulation profile, and chest and

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Table 12.1 Indications and contraindications of neonatal respiratory and cardiac ECMO

Inclusion criteria	Exclusion criteria
Severe respiratory failure	Severe brain damage
Severe hypoxia with acute decompensation (PaO_2 < 40 mmHg)	Significant intraventricular/ intracranial hemorrhage
Inadequate DO_2[a]	Lethal chromosomal disorder or anomalies
Sustained elevation of OI[a] (>40 for >4 h)	Irreversible organ damage (unless plan for transplant, e.g., cardiac transplant)
Severe pulmonary hypertension with or without RV failure	Neck vessels are too small to cannulate (unless considered for thoracic cannulation)
Congenital heart disease	Gestational age less than 34 weeks
Myocarditis/cardiomyopathy	Weight less than 2 kg
Arrhythmias	Uncontrolled bleeding, severe coagulopathy

OI: Oxygenation index = FiO_2 × mean airway pressure × 100)/PaO_2
[a]DO_2: Tissue oxygen delivery

abdominal radiographs should be obtained. Cranial ultrasound should be performed to establish a baseline view of the brain in the event an intraventricular hemorrhage occurs. An echocardiogram should also be undertaken to assess baseline cardiac structure and function to determine whether the neonate is eligible for EMCO and the mode of ECMO support that is most appropriate.

Given the need for systemic anticoagulation during ECMO, the risk of an intracranial hemorrhage (ICH), particularly in neonates, is substantial in light of the developing coagulation system and immature germinal matrix, particularly in premature neonates. This risk increases significantly with gestational age < 34 weeks [8, 9]. An earlier study demonstrated reduced survival and a greater rate of ICH in neonates <34 weeks' gestation compared with term neonates (63% vs. 84%, $p < 0.001$, and 37% vs. 14%, $P < 0.001$, respectively) [13]. Recent studies, however, reported improved survival and reduced morbidity in neonates <34 gestational age. It is reasonable to consider ECMO as a possible option for premature neonates on a case-by-case basis, once the risks have been identified and close monitoring is followed [14, 15].

Neonates who are small for gestational age (< 2 kg) carry a greater risk of intracranial bleeding and mortality. Their neck vessels may be too small to fit standard ECMO cannulae, although the neck vessels in neonates <2 kg have been cannulated successfully using thin-walled catheters or centrally (transthoracic cannulation) by draining blood directly from the right atrium (RA) (atrial appendage) and returning it to the aortic arch [16].

Prolonged mechanical ventilation before commencing ECMO could suggest irreversible lung disease. In some institutions, mechanical ventilation for more than 14 days is considered a relative contraindication for ECMO [17]. Accordingly, we suggest that patients who received more than 14 days of mechanical ventilation should be carefully screened once ECMO is under consideration. Few conditions such as alveolar capillary dysplasia, severe pulmonary hypoplasia, and surfactant protein B deficiency may present with severe hypoxic respiratory failure similar to more common reversible etiologies for respiratory ECMO. Neonates with these irreversible lung diseases may be placed on ECMO inadvertently before the diagnosis can be confirmed.

Cardiac ECMO describes the need for VA ECMO for cardiac and circulatory support. The number of neonatal cardiac ECMO cases in the ELSO registry has increased over the last 20 years [18, 19]. Neonates with congenital heart disease (CHD) may require ECMO support preoperatively to stabilize cardiac function, immediately postoperatively after failing to wean off CBP, or shortly after coming off CBP because of a persistent low cardiac output syndrome or arrhythmias [16]. Hypoplastic left heart syndrome represents the most common CHD for which ECMO has been salutary.

Neonatal myocarditis is another possible indication for ECMO support. However, diagnosing myocarditis in the neonate can be very difficult, with a prevalence that is not well described. Acute fulminant myocarditis may present with cardiogenic shock, left ventricular failure, and arrhythmias that require ECMO support as a bridge to recovery or transplantation [16, 20].

ECMO Circuit Components

The major components of any ECMO circuit include the cannulae, tubing, mechanical blood pump, and gas exchange device (membrane oxygenator). ECMO circuit design differs among institutions to suit their needs and patients' populations. In the last two decades, the safety and efficacy of ECMO have undergone major advances as described below.

ECMO pumps consist of two types: roller head (semiocclusive) pumps and centrifugal pumps. Roller head pumps were the standard of care for many years until the middle of the 2000s, at which time centrifugal pumps became more popular with improvements and advances.

Roller head pumps have more limited use in neonates in some centers, as they present a smaller risk of hemolysis compared with centrifugal pumps in neonates [1, 21, 22]. The blood is pressed forward through the tubing, "the raceway," against a plate in the pump housing at two pressure points while the pump is rotating. This provides continuous forward motion of the blood toward the oxygenator and then back to the body. The venous blood that flows into the pump (preload) flows by gravity; hence, the neonate must be positioned above (100–150 cmH_2O) the pump and the bladder reservoir to assure an efficient operation. Venous drainage

slows in the presence of several factors including hypovolemia, tamponade physiology (e.g., large pleural or pericardial effusion/hemorrhage, pneumothorax), or kinked tubing on the venous side of the circuit (premembrane). As a result, the pump will slow down or stop until the venous drainage is re-established or the cause of the problem is corrected.

Most of the present roller head pumps have servo-regulation capabilities that allow the ECMO specialists to set alarms to slow the pump flow when a threshold negative venous (access, premembrane) pressure is detected. This gives the specialist time to troubleshoot and address the problem without interrupting or stopping the pump flow.

In contrast, centrifugal pumps deliver flow using an afterload-dependent technique that utilizes rotatory forces generated by a rotating impeller. Centrifugal pumps are non-occlusive. The newer pumps utilize magnetic levitation to suspend and spin the impeller. Their blood-handling qualities have also improved, minimizing heat generation, hemolysis, and air cavitation. Blood enters these pumps at the apex and is expelled at the base toward the membrane oxygenator. These pumps are easy to set up, have small priming volumes, can trap air and debris within the vortex, and are independent of gravity for a steady drainage of blood. These pumps can be placed at any height relative to the patient, which makes them suitable for transport. Despite these favorable characteristics, several reports showed that neonates and young infants who are supported by centrifugal pumps have increased morbidity, ECMO complications (e.g., hemolysis), and mortality [21–24]. Nonetheless, centrifugal pumps can be safely used in neonates and infants who require ECMO support.

During ECMO, gas exchange occurs through the membrane oxygenator or artificial lung. There have been major advances and innovations in oxygenators over the last few decades. Initially, the only membrane oxygenator was a flat, reinforced silicone membrane envelope that was wound in a spiral coil around a polycarbonate spool. A highly gas-permeable membrane separated the blood and gas compartments, with no direct blood-gas interface. Gas transfer occurred by molecular diffusion as it does in the human lung. The design and quality of the silicone membrane oxygenator made it very effective for gas exchange. However, the compact design created a long blood path with high resistance, which proved difficult for priming and increased the risk of clot formation. Additionally, a separate blood warmer (heat exchanger) was added to these ECMO circuits to warm up the blood before it returned to the neonate. Silicone membrane oxygenators are no longer available for clinical use. A newer generation of devices, the hollow fiber oxygenators, became available in the 2000s. These oxygenators consisted of microporous material where gas exchange occurs by bulk gas transfer via a direct gas-to-blood interface. These devices proved easy to prime and exhibited efficient gas exchange, although the longevity of these devices was limited to a few hours. Plasma was known to leak into the gas phase causing these devices to fail prematurely and suddenly, requiring their urgent replacement.

The present oxygenators (e.g., Quadrox-iD, Maquet, Hirrlingen, Germany) have incorporated many of the advantages of earlier membrane oxygenators using polymethylpentene (PMP) and polyurethane fibers. The PMP is a microporous material that is very efficient for gas exchange over an extended period (weeks and months). These devices are durable and may attenuate the inflammatory response during the onset of ECMO. These devices have a low resistance to blood flow, which makes them easy to prime, reducing the potential for clot formations and early oxygenator failure. Contrary to previous designs, the new models are very efficient and durable [25]. Their rated flow (the volume of venous blood whose oxyhemoglobin saturation can be increased from 75% to 95% in a given period) is substantial, at 7 L/min. In most cases, a single oxygenator provides sufficient support for a child of any size or age for the entire ECMO run.

Several types of vascular catheters (cannulae) are available for neonatal ECMO support. Single lumen cannulae with different sizes are available for VA ECMO for the right internal jugular vein (RIJV) and carotid artery access. They are available in sizes from 8 to 14 Fr. These cannulae have wire-reinforced bodies that are designed to keep patency and prevent luminal occlusion. Venous cannulae have 3- to 4-centimeter-long multi-fenestrated flexible tips with side and end holes to augment venous drainage. In contrast, arterial-type cannulae have a single end hole for blood return via the aortic arch. Arterial cannulae are also used for cephalic venous drainage (cephalad drainage) in VV-V ECMO [26].

Double-lumen catheters are used to access the RIJV for VV ECMO. Blood is drained from both venae cavae to the RA toward the tricuspid valve. Until recently, the OriGen (Austin, TX) dual-lumen cannula was the most common cannula used for VV ECMO support in neonates. However, presently, this cannula is unavailable. Avalon Elite Bi-Caval dual-lumen catheters (Maquet, Hirrlingen, Germany) are not very commonly used in neonatal VV ECMO due to the risk of RA perforation and rupture [27, 28]. Recently, a newly designed Crescent™* RA jugular dual lumen catheter (Manufactured by MC3, Inc. Dexter, MI USA and exclusively distributed by Medtronic) are becoming available in the market to use for neonatal VV ECMO support.

Gas Exchange on ECMO

ECMO removes CO_2 and adds O_2 through an artificial lung (the oxygenator) by draining blood from the venous system through a cannula in the venae cavae and returning the bloods in the case of VA ECMO via the aorta through a cannula in

the common carotid artery or in the case of VV ECMO into the RA through a separate cannula or a separate lumen of the same cannula used for drainage (dual-lumen cannula) [9].

ECMO provides gas exchange via the oxygenator to permit caregivers time to confirm the underlying diagnosis and to institute treatment until the neonate recovers or the affected organ is replaced (e.g., cardiac transplant). This technique minimizes the risk of iatrogenic lung injury from high-pressure ventilator settings and/or inotropic and vasopressors' use.

The entirety of the gas exchange occurs in the oxygenator. The patient's arterial oxygenation is an admixture of ECMO blood and native venous blood. Gas exchange should not be managed by adjusting the mechanical ventilator, as the lungs are placed on rest settings oaor the trachea is extubated while on ECMO support.

To understand ECMO and to manage patients on ECMO, we must understand the kinetics of O_2, its delivery, and O_2 consumption.

Oxygen delivery (DO_2) is the amount of O_2 delivered to peripheral tissues each minute, which depends on the lungs, blood, and circulation. DO_2 equals the O_2 content (CaO_2) times the cardiac output/index ($DO_2 = CaO_2 \times CI = 600$ mL O_2/min/m^2). CaO_2, the amount of O_2 carried by the hemoglobin (Hb), is best represented by this equation: $CaO_2 = (1.36$ cc/gm $\times SaO_2 \times$ Hb g/dL) + ($PaO_2 \times 0.003$ ccO_2/mmHg/dL), where SaO_2 is the patient's arterial saturation and PaO_2 is the arterial partial pressure of O_2. O_2 consumption (VO_2) represents the amount of O_2 demand of the body and is determined by tissue metabolism. O_2 demand decreases with rest, sedation, muscle relaxation, and hypothermia and increases with infection, fever, catecholamines, and muscle activity. The normal VO_2 in neonates is 5–8 mL O_2/kg/min, in children 4–6 mL O_2/kg/min, and in adults 3–5 mL O_2/kg/min. DO_2 is three to five times greater than the VO_2 with a large reserve in supply. Using the Fick principle, the amount of O_2 absorbed during gas exchange is equal to the amount of O_2 consumed by peripheral tissues during metabolism regardless of the status of pulmonary function. The VO_2 reflects the metabolic demand, a variable that is independent of the O_2 supply. So, mild to moderate reduction in DO_2 is well tolerated and does not compromise VO_2. As DO_2 decreases further, the O_2 extraction increases until it can no longer maintain the VO_2. At this point, tissue hypoxia occurs leading to multiorgan failure and death. In VA ECMO, mixed venous O_2 saturation (SvO_2) is an excellent indicator of adequate DO_2, with a goal of achieving 65–80%. SvO_2 is interpreted differently in VV ECMO as it indicates premembrane saturation as a monitor of recirculation, i.e., that portion of oxygenated blood draining from the patient to the ECMO circuit that was just delivered to the patient's RA.

The efficiency of oxygenating blood in the membrane lung depends on several factors including the amount of O_2 that can be added to inlet blood, Hb, blood flow, surface area and oxygenator membrane permeability, and rated flow.

CO_2 removal in the ECMO circuit depends on the oxygenator membrane permeability, the membrane surface area, and mainly the oxygenator ventilation gas flow (the sweep gas). The CO_2 diffusion coefficient is at least six times greater than that of O_2, so even with a smaller gradient, CO_2 can be removed easily via the ECMO circuit. Increasing the sweep gas flow (analogous to adjusting the minute ventilation on a ventilator) and the total surface area of the oxygenator in the ECMO circuit can selectively transfer more CO_2, with less effect on O_2 delivery [29].

The output of the ECMO circuit is determined by the amount of venous blood that is withdrawn from the venous reservoir. In roller head pumps, venous drainage is gravity-dependent, with the driving force being the difference in the height of the column of blood in the venous cannula and the bladder. Several factors can affect venous drainage including hypovolemia, kinking or constriction of the circuit lumen, clotting of the venous cannula, and patient's tamponade physiology (e.g., pneumothorax and pneumopericardium).

In VA ECMO, DO_2 is controlled by the combination of blood oxygenation in the oxygenator, the flow through the circuit, O_2 uptake through the native lung, and the cardiac output through the native heart (total $DO_2 = DO_2$ via ECMO + DO_2 via the native heart). When choosing the size of the circuit and the extracorporeal flow, it is important to assume that there will be a complete bypass of the native heart (i.e., no gas exchange across the lungs and the native heart).

During VA ECMO, some venous return enters the patient's pulmonary circuit. In the diseased lung, this blood will remain poorly oxygenated. As it admixes with the well-oxygenated blood from the ECMO circuit in the aortic arch, arterial desaturation may occur. The blood that is in the LV is identical to the blood in the RA, typically with a saturation of 75% and a PaO_2 of 35 mmHg. The blood that emerges from the ECMO circuit is 100% saturated with a PaO_2 of about 400–500 mmHg. So, the resulting PaO_2 and CaO_2 will reflect the relative amounts of the circuit and the native lung/heart flow.

In VA ECMO, an increase in systemic PaO_2 may indicate improving lung function or decrease in native cardiac output given the ECMO flow is constant. It may also reflect an increase in ECMO flow with no change in lung and cardiac function.

Increasing the FiO_2 in the ECMO circuit may increase the saturation but only to a limited extent.

The VA ECMO pump creates a nonpulsatile flow. As more blood is routed through the ECMO circuit, the systemic arterial pulse contour becomes flatter, and the pulse pressure becomes narrower. If complete bypass is achieved, the arterial contour will be flat, and the pulse pressure will be <5 mmHg.

VA ECMO places the oxygenator in parallel with the native lungs and provides both cardiac and pulmonary support. In contrast, VV access places the oxygenator in series with the native lung and provides only pulmonary support. For full support, ECMO blood flow is about 80–100 mL/kg/min. With that target flow in mind, cannula size selection is imperative to ensure successful ECMO support [10].

Modes of ECMO

The primary modes of ECMO used in neonates are VA and VV ECMO. In VA ECMO, blood is drained from the venous system, mainly the RA, to the ECMO circuit and returned to the arterial circulation via the aorta. In VV ECMO, blood is drained from the venous system, usually the venae cavae, and returned to the venous system, via the RA [1, 29, 30]. This commonly occurs with double-lumen 13 Fr and 16 Fr cannulae. Additional venous drainage can be obtained in VA and more commonly in VV ECMO using a cephalic drainage catheter [26].

VA ECMO provides cardiac and pulmonary support, so it is suitable for cardiac failure, myocarditis, and postoperative congenital heart surgery. It is commonly used in neonates with CDH who require ECMO for severe pulmonary hypertension and/or RV failure.

VA ECMO provides several advantages including rapid stabilization and circulatory and cardiac support; however, it requires ligation of the carotid artery, increases in left ventricular afterload, and increases in the risk of systemic emboli especially cerebral ischemic strokes. Alternately, VV ECMO maintains pulmonary blood flow with oxygenated blood, which relaxes the pulmonary vasculature and decreases pulmonary vascular resistance, provides oxygenated blood to the coronary circulation and myocardium, and minimizes and sometimes eliminates the risk of systemic embolization [1].

ECMO Management

Cannulation and ECMO Initiation

A thoughtful cannulation strategy and optimal placement of the cannulae are critical to ensuring successful ECMO support for better patient outcomes and fewer complications. Cannula selection depends on the mode of ECMO used (i.e., VA versus VV), patient size and age, and vessel size and patency. Cannulation methods vary from open surgical technique to percutaneous approach depending on the patients' characteristics, mode of ECMO, and physician and institutional experience [31].

In neonatal VA ECMO, direct (peripheral) cannulation of the right common carotid artery and RIJV via an open surgical technique is the most used method of cannulation. Initially, the infant is properly positioned by placing a small roll under the shoulders to extend the neck slightly with the face turned to the left. An X-ray plate is placed under the neck and chest if possible. After establishing intravenous access, securing an endotracheal tube, and prepping the skin, a sterile field is created. A transverse incision is made 1 cm superior to the right clavicle, and the tissue plane between the heads of the sternocleidomastoid muscle is dissected, exposing the carotid sheath that contains that common carotid artery and the vagus nerve. Care must be taken to avoid any irritation or damage to the vagus nerve while dissecting the artery. Intensivists should be aware that bradycardia with hemodynamic instability can occur during dissection, which can be prevented by infiltration with local anesthesia or by administering atropine. The RIJV is also identified at this time. The vessels are usually tied cranially (distally), and a vascular clamp is applied proximally. Unfractionated heparin (UFH) (50–100 unit/kg) is given as a bolus a few minutes before creating the venotomy and arteriotomy incisions. Each catheter is then advanced one at a time. Care must be taken while advancing the catheters to avoid damaging or dissecting the vessels. The venous cannula is advanced until the tip rests in the middle of the RA, whereas the arterial cannula is advanced until the aortic arch is reached. The arterial cannula can point toward the ascending aorta but must not encroach on the aortic valve. Accurate placement of the arterial cannula is critical as the coronary arteries perfuse the myocardium via retrograde flow from the tip of the arterial cannula. The neonatal/pediatric VA ECMO cannulae are available in four sizes, from 8 to 14 Fr catheters. Venous cannulae have several side holes in addition to a distal drainage site (https://www.medtronic.com/content/dam/medtronic-com/products/cardiovascular/cannulae/documents/pediatric-cannula-catalog.pdf). These cannulae are wire reinforced throughout, which reduces the risk the cannula will collapse or kink [1, 9, 10]. The femoral vessels are not commonly cannulated in neonates or infants because they are too small to support adequate gas exchange and circulation, in addition to the risk of limb ischemia.

Transthoracic (central) cannulation is used after congenital heart surgery if the neonate fails to wean off CPB. The ECMO circuit employs the preexisting cannulae used for CPB. In general, central cannulation allows the use of larger cannulae that are needed to provide larger than usual ECMO flow (e.g., 200 mL/kg/min) for complete cardiac support [16, 31–33]. It is not unusual to use a left atrial (LA) cannula on the venous side of the circuit, thereby increasing the venous drainage from the ECMO circuit. This vents the left side of the heart to allow 100% bypass, giving the myocardium time to recover after CPB or circulatory arrest without the need for LV to empty blood from the native pulmonary venous return, bronchial veins, or thebesian venous drainage to the

LA [16]. This venting is important to prevent subendocardial ischemia and pulmonary edema. Other techniques used, include septostomy, or inserting a superior pulmonary venous cannula, a peripheral cannula through the atrial septum into the LA, or by placing a vent through the LV apex. Short of septostomy, the other techniques are primarily in older children and adults [16, 31].

Recently, a few reported the use of central cannulation in patients with severe refractory septic shock with promising results [34, 35].

In neonatal VV ECMO, vessels may be cannulated through a percutaneous Seldinger technique. This is best performed using ultrasound guidance to assure the optimal size of the cannula and proper visualization of the vessel before inserting the cannula. This commonly occurs when a double-lumen 13 Fr and 16 Fr cannula is used. Additional venous drainage can be obtained in VV ECMO using a cephalic drainage catheter placed in a retrograde fashion via the RIJV (Fig. 12.1).

Venous cannulation in VV ECMO can also be achieved through a semi-percutaneous approach using a modified Seldinger technique. This has been described by initially making a transverse incision 2 centimeters (cm) superior to the right clavicle to expose the anterior surface of RIJV [36]. Once the vessel is exposed, an angiocath is placed through the skin 2 cm superior to the incision, the needle is introduced into the vein using the Seldinger technique, a guidewire is advanced, UFH bolus is given, the dilating catheter is advanced, and, lastly, the double-lumen cannula is advanced over the guidewire into the RIJV with the tip resting within the RA when the OriGen catheter (Austin, TX) or the Crescent™* RA jugular dual lumen catheter (MC3 Dexter, MI USA) are used or within the IVC when the Avalon Elite Bi-Caval dual-lumen catheter (Maquet, Hirrlingen, Germany) is used. With the lack of availability of the OriGen catheter and myocardial perforations associated with the use of the 13 Fr Avalon Elite Bi-Caval dual-lumen catheter [28], many institutions are using VA ECMO support instead of VV ECMO for acute respiratory failure. Nonetheless, a few ECMO centers continue to use the 13 Fr Avalon Elite Bi-Caval dual-lumen catheter for neonatal VV ECMO respiratory support [37]. The Crescent™* RA jugular dual lumen catheter (MC3 Dexter, MI USA) is a promising cannula to use for neonatal VV ECMO support.

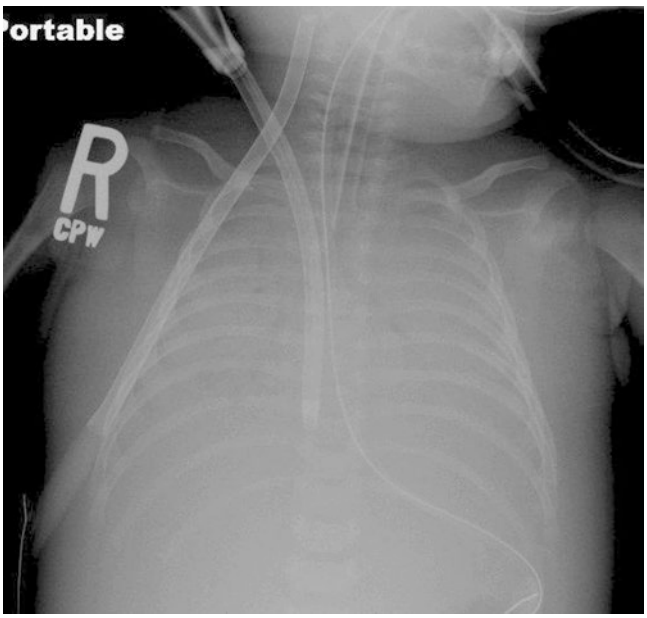

Fig. 12.1 Double-lumen VV cannula with a cephalad cannula in a neonate

Anticoagulation and Homeostatic System in Neonates

The extracorporeal circuit disrupts the normal balance of coagulation and fibrinolysis by exposing large amounts of blood to non-endothelial surfaces. This leads to activation of coagulation, fibrinolysis, and acute inflammatory responses, with the coagulation cascade shifting the hemostatic balance to a hypercoagulable state, thus requiring systemic anticoagulation [38–40].

Despite the improved technology, increasing clinical practice and experience, and better monitoring, hemorrhagic and thrombotic events remain the most common causes of morbidity and mortality in neonates supported with ECMO. The risk of hemostatic complications in neonates is greater than that in older children and adults. This is related to the developing hemostatic system and immature germinal matrix, especially in premature neonates.

Although all components of the hemostatic system are present at birth, important differences exist among neonates. Platelets play a pivotal role in primary hemostasis. The platelet count and size do not differ in neonates compared with adults, although the platelet response to agonists decreases in neonates and tends to be hypoactive. However, neonates have greater plasma concentrations of von Willebrand factor (VWF), a greater hematocrit, and a greater percentage of large VWF multimers, which adhere more to platelets [41]. All these elements may explain the shorter bleeding time in neonates compared with older children and adults.

Secondary hemostasis consists of a series of interactions of coagulation factors that lead to an insoluble fibrin clot. The liver and endothelial cells of the fetus are responsible for producing coagulation factors early in gestation with increasing plasma levels by birth. Nonetheless, the plasma levels of most of the procoagulant and anticoagulant factors are decreased at 50% of the levels in older children and adults. So, with this immature hemostasis system in neonates, ill-

nesses (e.g., sepsis) and other stresses, including exposure to the ECMO circuit, may disrupt the hemostasis system leading to severe consumptive coagulopathy that triggers bleeding and thrombosis [11].

Intravenous continuous infusion of UFH is the present standard of care for anticoagulation in neonatal ECMO. Maintaining the patency of the ECMO circuit is critical to preventing both circuit and patient vascular thromboses [42].

UFH is a complex glycosaminoglycan that blocks clot formation by binding to antithrombin (AT), an endogenous anticoagulant produced by the liver, to inhibit factors Xa and IIa. Binding results in a conformational complex that increases the inhibitory activity of AT by more than 1000-fold, inactivating the free, unbound thrombin, thereby preventing further clot formation.

At the time of ECMO cannulation, intravenous UFH (50–100 units/kg) is given just a few minutes before placing the cannulae in the vessel(s), followed by a continuous IV infusion starting at 20–25 units/kg/h to continue the anticoagulation. The anticoagulation is closely monitored using the activated clotting time (ACT), prothrombin time (PT), activated partial thromboplastin time (aPTT), fibrinogen levels, platelets, AT levels, and anti-factor Xa [39, 40]. The UFH infusion is adjusted to maintain an appropriate level of anticoagulation.

ACT is a bedside, point-of-care test that measures the time for a sample of whole blood to clot when exposed to an activator such as kaolin or celite. The target range for anticoagulation varies with the institution, the laboratory analyzer, activator used, and test indication. These devices need to be calibrated frequently to avoid major discrepancies. The target range for the ACT in neonates on ECMO varies from 180 to 200 s for older devices and 150 to 170 s for newer devices.

Thromboelastography (TEG) is one of the global assays of coagulation that measures the viscoelastic properties of blood and provides information on clot dynamics and fibrinolysis. TEG can detect deficiencies in the hemostasis process throughout the coagulation cascade with more information about initial clot formation, clot acceleration, maximum clot strength, and fibrinolysis. TEG technology and expertise are not widely available, and its value in monitoring anticoagulation in neonates on ECMO has neither been studied nor established [38].

Despite a better understanding and more advanced monitoring of anticoagulation management in ECMO, a paucity of high-quality research and evidence on the most effective and safest methods of anticoagulation in neonates persists. To manage anticoagulation well, it is important to understand which aspect of the coagulation cascade each test analyses and the threshold for abnormal values. This is in addition to understanding all details related to the patient clinical status including number of days on ECMO, presence of bleeding, clots in the ECMO circuit, hemoglobin levels, UFH dose and recent adjustments, recent and upcoming procedures, and recent transfusions. After assimilating all of this information, providers should understand how to address any abnormal result and titrate the anticoagulation therapy to meet the desired targets [43–45].

Direct thrombin inhibitors (DTIs) have been increasingly used to anticoagulate on ECMO, especially adults and older children. Their use in neonates is limited to rare occasions of UFH resistance, allergy, or heparin-induced thrombocytopenia (HIT). DTIs such as bivalirudin and argatroban bind both the free circulating and fibrin-bound thrombin. They bind directly to either the catalytic site or both the catalytic site and exosite-1 on thrombin. Additionally, DTIs are independent of AT, selectively binding to thrombin and not to other circulating plasma proteins, which make them more effective, with consistent and predictable effects [39].

Mechanical Ventilator Management

In neonatal respiratory failure, ECMO supports gas exchange and provides the opportunity to minimize the risk of ventilator-induced lung injury. Despite the positive impact of a protective and gentle lung ventilation strategy on survival in acute respiratory failure in neonates, children, and adults, there is limited evidence to guide the ideal lung "rest" mechanical ventilation strategies in neonates while receiving ECMO support. Practice variations in the use of lung rest ventilator settings during ECMO for neonatal respiratory failure vary widely [46–49].

Conventional mechanical ventilation (CMV) is used in the vast majority of neonatal ECMO with pressure control mode being the most common mode [49].

Pressure control mode maintains plateau pressures ≤20 cmH_2O, thereby preventing large swings in PIP that may occur while using a volume control mode. It also allows serial monitoring of lung compliance and tidal volume during lung recovery.

Gentle ventilation or "rest ventilator" settings have been widely adopted in many ECMO centers in recent years [47]. However, there is variability in mechanical ventilator practices while on ECMO. Serial daily monitoring of plateau pressure, compliance, and tidal volume may offer valuable information. Generally, the approach consists of low ventilator rates, five to ten breaths per minute, moderate positive end expiratory pressure (PEEP), 4–12 cmH_2O, and low peak inspiratory pressure (PIP) ≤ 20 cmH_2O and FiO_2 of 0.21–0.4 [49]. Although the only randomized trial reported that a PEEP of 12–14 cm H_2O was favorable compared with a PEEP of only 4–6 cm H_2O and decreased the duration of ECMO by an average of 34 h [50], neonatal critical care and ECMO today differs significantly from 25 years ago when the study was conducted in that VA ECMO was the main mode of ECMO and mechanical ventilation equipment and strategies differed.

High-frequency oscillatory ventilation (HFOV) is also used in neonatal ECMO. It is preferred in cases of severe air leak syndrome, severe pulmonary edema, and pulmonary hemorrhage. HFOV ventilation settings (amplitude and frequency) should be set to minimum values. Similarly, lung rest strategies should be followed with a mean airway pressure $\leq$ 20 cmH_2O and a maximum pressure of 25 cmH_2O being implemented. It is uncommon to use HFOV during ECMO support; its use could make it difficult to perform pulmonary toilet and assess tidal volumes and lung compliance, in addition to the need for heavy sedation and neuromuscular blockade.

Continuous positive airway pressure (CPAP) with pressure support (PS) is a modality that is presently more acceptable especially in awake patients with or without tracheostomy but less in neonates and infants. In adults, CPAP can facilitate early extubation after ECMO course.

Sedation and Analgesia

Optimal sedation and analgesia during ECMO in neonates remain unclear. Many studies have demonstrated the need to escalate sedation requirement during ECMO because of an increase in the volume of distribution, increased sequestration of drugs in the ECMO circuit tubing and oxygenator, and decreased metabolism. ECMO support can have a substantial impact on drug disposition, and dosing is likely different in children on ECMO. Dexmedetomidine, midazolam, fentanyl, hydromorphone, morphine, and ketamine are the most used sedatives in pediatric patients during ECMO. In this section, we will discuss mainly fentanyl, morphine, and midazolam as they are the most studied sedatives for neonates and infants on ECMO.

During ECMO, the volume of distribution (Vd) of all drugs is increased. The disposition of drugs during ECMO depends on several factors including their lipophilicity and percentage of protein binding [51, 52]. The more lipophilic and the greater protein binding, the more drug extraction occurs. Additionally, clearance (CL) is generally decreased, resulting from underlying renal and/or hepatic dysfunction in children who require ECMO. In aggregate, these factors require a significant increase in the dose of sedatives and analgesics used after initiation of ECMO that may require further adjustment during ECMO as organs recover and CL of the medications increases.

Fentanyl is significantly extracted during ECMO because it is very lipophilic, is highly protein-bound (80–85%), and has a strong affinity for the membrane oxygenator [53, 54]. This translates into substantially larger doses with the onset of ECMO, an effect that is compounded by possible tolerance to fentanyl [51, 55].

Morphine is not as lipophilic as fentanyl and only 30–40% protein-bound [56]. The Vd of morphine is increased due to drug extraction during ECMO [57]. This may necessitate larger initial doses of morphine after initiation of ECMO to achieve the desired level of analgesia and sedation. Morphine may be preferable to fentanyl for analgesia in ECMO as the latter is more highly extracted by the ECMO circuit. However, unlike fentanyl, morphine has active metabolites with prolonged half-lives, especially in neonates, which may make its use less predictable.

Midazolam is highly lipophilic and highly protein-bound (97%). It is highly extracted by the ECMO circuit. Vd and CL of midazolam are greater during ECMO. Accordingly, the dose requirement for midazolam for sedation increases after the start of ECMO [58]. The use of a centrifugal pump, circuit priming with albumin, and older used ECMO circuits reduce the extraction of midazolam by the ECMO circuit [51, 59]. The dose of midazolam will have to be adjusted throughout the ECMO period based on these factors.

Dexmedetomidine is used increasingly as an adjunct sedative in pediatric and neonatal populations. Despite the limited evidence, data suggest that dexmedetomidine is moderately extracted by the ECMO circuit, requiring larger doses to achieve therapeutic plasma concentrations in patients supported by ECMO [60, 61].

Fluid Management

Maintaining a strict fluid balance in neonates supported on ECMO is crucial. Fluid overload has been associated with increased morbidity and mortality. It is not unusual to require a large volume of fluids at the initiation of ECMO because acute inflammation and capillary leak require large amounts of colloid and crystalloid fluid resuscitation for the first 24–48 h. Fluids should be infused with great care and aim for dry weight once hemodynamic stability is achieved [62]. The use of diuretics, concentrating medication infusions, and the early initiation of ultrafiltration and CRRT are useful maneuvers to remove fluids and reduce the duration of ECMO and the ICU length of stay [8, 63].

Decannulation

Decannulation is undertaken to separate the neonate from the ECMO circuit. It should be considered when the neonate's underlying pathology has improved, lungs have been recruited, and only minimal ECMO flow is required to maintain gas exchange and hemodynamic support. Decannulation is typically performed in the ICU but can also be performed in the OR [64]. A "trial off" ECMO is conducted once the criteria for improvement have been met. This entails separating the neonate functionally from the ECMO circuit by briefly clamping the draining and return tubing closer to the

patient and monitoring the gas exchange and hemodynamics without ECMO support while discontinuing flow from the neonate to the circuit. This is typically performed in the case of VA ECMO patients from a few minutes to 30 min while sporadically maintaining patency of the cannulae. Once this is deemed to be successful, the ECMO support is resumed at minimal flow to maintain the integrity of the ECMO circuit while providing minimal or no support for the patient. It is not uncommon to separate the oxygen source from the oxygenator during that period. VV ECMO trialing off does not require that the cannulae be clamped. This can be achieved by reducing the ECMO flows and separating the oxygen source from the oxygenator for 2–6 h or longer, the sweep gas is turned off, and the oxygenator is capped, thereby eliminating gas exchange across the oxygenator. This "trialing off" interval is deemed neonates is surgical site bleeding to be successful if gas exchange is maintained during this period. Echocardiography might be needed during these trials if an assessment of myocardial function or RV pressure is required to establish the patient's readiness for decannulation.

Communication among the multidisciplinary personnel is important. This includes the ECMO specialist, the intensive care physicians, nursing staff, respiratory therapist, the surgeon, and the OR staff [12]. Typically, neck vessels are ligated distally; however, a few reported carotid artery repair safely after decannulation [65].

Complications

Bleeding and thrombosis remain the most common complications of ECMO. Bleeding at the ECMO cannulation site, surgical site bleeding, and ICH are the most common complications. The most common hemorrhagic event in neonates is surgical site bleeding (12.4% respiratory and 29.1% cardiac), followed by cannula site bleeding (18.2% respiratory and 10.7% cardiac) and lastly gastrointestinal (4.2% respiratory and 1.1% cardiac). ELSO defines bleeding events as those resulting in a transfusion of more than 20 mL/kg per day or 3 units per day in either the gastrointestinal, pulmonary, cerebral, peripheral/mediastinal cannulation site, or surgical sites.

ICH is the most devastating complication of ECMO and is associated with high mortality and morbidity [66]. Severe ICH is the most common cause of death in neonatal ECMO and is associated with poor outcomes in survivors. Pre-ECMO factors which may increase the risk for ICH include asphyxia, severe hypoxia, hyperventilation, hypoventilation, metabolic acidosis, multiorgan failure, sepsis, and hypotension [9, 18]. While neonates are on ECMO, several factors may contribute to bleeding complications including anticoagulation therapy, surgical causes, and consumptive coagulopathy that is either related to the ECMO circuit or the patient's underlying disease [11].

Thrombosis and clots in the ECMO circuit (oxygenator, bridge, bladder, hemofilter, or others) are the most common mechanical complication for neonatal respiratory and cardiac ECMO support. Thrombotic complications are defined as those that result in mechanical failure such as thrombosis in the circuit component (e.g., oxygenator). About 20% of patients require a circuit change or change of components due to thrombotic issues.

Other complications include cannula dysfunction, seizure disorders, renal failure, and infection [67].

Survival and Outcome

Neonates on ECMO are at risk for several complications as mentioned earlier especially neurological injuries including ICH, embolic strokes, and seizures. In addition to a greater mortality in patients with these complications [9, 66, 67], previous studies reported major disabilities, including developmental delay, cerebral palsy, and visual or hearing loss, among survivors [68].

Based on the ELSO registry data, the overall survival to hospital discharge is 73% for neonates treated with ECMO for respiratory disease. However, the overall survival rate to decannulation from ECMO support is even greater, 83% [8]. The average ECMO run times have increased 33% during the last 15 years from 150 h in the 1990s to more than 200 h per ECMO run. This can be attributed to offering ECMO support to more complex critically ill patients with more associated comorbidities. This has been born out in a recent report in which neonatal ECMO for respiratory indications was reduced by one-third, whereas ECMO use for patients with complex diagnoses such as CDH along with prolonged ECMO runs was increased, combined with significantly decreased survival [69].

Anesthesia Considerations for a Surgical Procedure on ECMO

Several issues should be considered by the anesthesiology team before commencing anesthesia/sedation for a neonate on ECMO [70]. The anesthesiologist should be aware of the patient's medical status including the severity of the cardiorespiratory conditions, the ECMO strategy, and procedure factors as outlined in Table 12.2.

Table 12.2 Anesthesia preparation for ECMO procedure

Patient/ECMO parameters
Indication for VA/VV ECMO
Present ECMO parameters
Cardiac support/inotropes/vasopressors
Anticoagulation parameters and therapy
Sedatives and their dosing
Procedure
Operative plan
Intraoperative anticoagulation plan
Intraoperative ventilation plan
Plan for transfer to operating room if indicated
ECMO, is decannulation with procedure anticipated?
Strategy to wean from ECMO
Parameters to initiate weaning and to abort weaning
Post-ECMO anticoagulation strategy
Post-ECMO ventilation strategy

Intraoperative Conduct of Anesthesia

In most cases, sedation for ECMO is achieved using systemic opioids, in doses that may require adjustment during ECMO if opioid tolerance develops. Tolerance may also apply to other commonly used ICU sedatives such as benzodiazepines and dexmedetomidine. Propofol may be used for both sedation and general anesthesia, although its high lipid solubility, substantial absorption by the ECMO circuit, and unpredictable blood levels limit its appeal. Furthermore, propofol infusion syndrome is a potentially fatal threat that is best avoided in neonates and infants, especially when associated with a systemic inflammatory condition and prolonged propofol infusions [71]. Inhalational agents such as isoflurane may also be used with specialized ICU ventilators (Maquet) to confer sedation or general anesthesia [72]. Neonates on ECMO are often paralyzed, not to improve ventilator compliance, but to avoid movement that could affect the position of the cannulae, thereby reducing venous return and/or obstructing arterial outflow. If a procedure will be performed, then paralysis or a deeper level of anesthesia may be required.

Transfer of Neonates to the Operating Theater

In many circumstances, the operative procedure can be completed in the PICU setting with the appropriate lighting, operating room staff, and surgical equipment. However, if the neonate on ECMO must be transferred to the operating room, this can provide some significant challenges in managing these patients.

The practical considerations for moving such a patient with precarious large-bore cannulae in the neck who depended on ECMO for gas exchange and circulatory stability and possibly multiple infusion pumps to support the neonate's circulation and anesthesia may be overwhelming. Before commencing a transport, a portable ECMO power supply such as a battery pack with hand cranking ability must be provided. All infusions should be reviewed and consolidated; only essential infusions and their pumps should be included in the transport. Each infusion line should be labeled before banding the multiple lines together to preclude them from becoming entangled. Bulky equipment including the ventilator/oxygenator, gas supply, and infusion pumps with battery supplies should be consolidated as much as possible as it may present challenges passing through doorways and into elevators. A care provider will be required just to monitor the cannula positions and warn of and prevent any potential accidental catheter movement or removal.

Monitoring During ECMO and Surgical Procedure

Anesthesiology and/or the critical care team usually care for these patients during the critical period before commencing ECMO and during cannulation, surgical procedures, and decannulation. Invasive blood pressure should be monitored during ECMO as well as during all surgical procedures while the neonate is on ECMO.

Mean arterial pressure (MAP) should be maintained within normal limits using either noninvasive or invasive monitoring. Intraoperative hypotension may be corrected by increasing the ECMO flow in case of VA ECMO support, by IV fluid administration, and/or by inotropic and vasopressor support especially in cases of severe vasodilation/vasoplegia and low systemic vascular resistance (SVR) [73]. Even with high levels of VA ECMO support, there should be a degree of pulsatility if the patient's myocardium is healthy and the LV is emptying its stroke volume via a normal aortic valve. If pulsatile flow is absent, then the LV may become overdistended, leading to myocardial ischemia. Other causes of decreased pulsatility include mechanical obstruction, severe hypovolemia, right-sided heart failure, or arrhythmias.

Blood gas samples should be analyzed frequently during ECMO and "on" pump procedures. In the case of VA ECMO, oxygen delivery is determined by several factors including the membrane oxygenator function and ECMO flow rate and to a lesser extent the native lung function and ventilator settings which would have a greater role in gas exchange during the lung recovery phase.

With the neck vessels cannulated, 50–80% of the total cardiac output is diverted to the ECMO circuit, while the remainder passes through the neonate's native heart and lung. The distribution of the blood flow depends on the amount of ECMO flow, cannula sizes, and native cardiac function. ECMO blood that is returned to the neonate mixes with blood in the aorta.

With VV ECMO, the ECMO blood mixes with the systemic venous return in a phenomenon called recirculation. This is determined by the type of cannulation, position of the cannula(e), cardiac function, and fluid status of the patient. The percent of blood that is recirculated is acceptable if systemic saturation exceeds 80%. The premembrane saturation is 10–20 percent less than the systemic saturation. As the lung recovers, the systemic arterial saturation (SaO_2) increases.

Oxygen delivery (DO_2) and oxygen content (CaO_2) are more important parameters of oxygenation than simply the SaO_2. DO_2 is the amount of oxygen delivered to peripheral tissues each minute. It depends on the lungs, blood, and circulation, and it is the product of CaO_2 and cardiac index (CI) $DO_2 = CaO_2 \times CI = 600$ mL O_2/min/m^2. Clinical indicators of adequate DO_2 are important to monitor regularly. Appropriate neurological examination, organ recovery, the absence of lactic acidosis, and an adequate urine output are markers of an adequate DO_2 that providers can easily evaluate at the bedside. SvO_2 can be very helpful when available to monitor DO_2 and oxygen consumption status in VA ECMO. When the SvO_2 exceeds 70%, it suggests an adequate DO_2 given proper venous cannula placement and $SaO_2 > 90\%$. In VV ECMO, premembrane (venous) saturation is helpful to detect recirculation but cannot be used to assess DO_2 as it does in VA ECMO.

Central venous pressure (CVP) is another important monitor used during both VA and VV ECMO. A sudden increase in CVP could indicate an urgent process such as tension pneumothorax and pericardial and pleural tamponade.

The neonate's temperature should be monitored continuously throughout the ECMO run. The ECMO circuit usually maintains the blood temperature at 37C using a water bath heater. However, if the patient is decannulated, this benefit will be lost, and other strategies to maintain an acceptable core temperature must be used. This is especially important as hypothermia may worsen the coagulation status, leading to intraoperative bleeding. Urine output is also a useful monitor of renal perfusion; however, if diuretics are used, the urine output cannot be used to monitor renal function. As a result, urine output may depend more on the dose of the diuretic than on the blood volume/fluid status. Also, some patients may require dialysis/ultrafiltration to remove excess fluid. These patients may have reduced native urine output during this treatment. Reducing tissue edema is important to improve the conditions for surgery and assist with weaning from the ventilator in the postoperative period. Serial monitoring of hemoglobin, blood gas analysis, coagulation status, and electrolytes is important for several reasons. It is important to replace cardiac protective electrolytes as needed and correct acid-base disturbances to optimize cardiac function. Also, monitoring the coagulation status is critical to minimize the risk of intraoperative bleeding and to help to guide the need for blood transfusions during the procedure.

Table 12.3 summarizes some of the more common emergencies and clinical scenarios that may arise at the bedside of a child on EMCO, the clinical presentations, and proposed management strategies.

Table 12.3 Troubleshooting common clinical problems and emergencies on VV and VA ECMO

	VV ECMO		VA ECMO	
Problems	Presentation	Management	Presentation	Management
Pneumothorax, large pleural effusion, large hemothorax, pericardial tamponade	– Interruption of ECMO venous drainage – Worsening negative ECMO venous pressures	– IV fluid boluses – Chest tube placement – Pericardial tube placement	– Interruption of ECMO venous drainage – Worsening negative ECMO venous pressures	– IV fluid boluses – Chest tube placement – Pericardial tube placement
Dehydration/ over-diuresis	– Hypotension and tachycardia – Interruption of ECMO venous drainage – Recirculation (small RA)	– IV fluid replacement	– Hypotension and tachycardia – Interruption of ECMO venous drainage – Narrow pulse pressure	– IV fluid replacement
Myocardial dysfunction	– Hypotension and tachycardia – Narrowing pulse pressure – Lactic acidosis – Multiorgan failure	– Inotropes and vasopressors – Change to VA ECMO	– Narrowing pulse pressure – Tachycardia (may be hypotension)	– Inotropes – Increase ECMO flow
Ventricular arrhythmias (non-perfusing VT, VF)	– Cardiac arrest – Circulatory collapse	– CPR, PALS – Change to VA ECMO	– Flat arterial line waveform – Slight decrease in blood pressure	– Increase ECMO flow if hypotension – No chest compressions – Anti-arrhythmic medications (e.g., amiodarone)

(continued)

Table 12.3 (continued)

	VV ECMO		VA ECMO	
Problems	Presentation	Management	Presentation	Management
Bleeding at cannulation site	– Hypotension and tachycardia – Interruption of ECMO venous drainage if bleeding is significant	– Blood transfusion – Address surgical intervention for stopping the bleed – Proper correction of thrombocytopenia and coagulopathy	– Hypotension and tachycardia – Interruption of ECMO venous drainage if bleeding is significant	– Blood transfusion – Address surgical intervention for stopping the bleed – Proper correction of thrombocytopenia
Thrombosis (clots in the oxygenator and ECMO circuit)	– Other than visual presence of clots in the tubing and the oxygenator, usually no symptoms. May cause oxygenator failure (i.e., patient hypoxemia)	– On venous side: no action is required if the oxygenator is working – On arterial side: may plan to change the circuit if planning for a longer run on ECMO	– Similar to VV ECMO except for high risk of systemic embolization and stroke if clots are on the arterial side (post-pump) of the ECMO circuit	– Immediate attention and plan to replace ECMO circuit if clots are on the arterial side
Pump failure	Sudden loss of ECMO flow and support resulting in severe respiratory insufficiency	Manual (hand crank) operation of the ECMO pump until power restored or pump replaced	Sudden loss of ECMO flow and support resulting in severe cardiorespiratory insufficiency	Manual (hand crank) operation of the ECMO pump until power restored or pump replaced
Extubation (loss of airway), ventilator failure.	No change given ECMO support is adequate	– No action needed, may choose to reintubate (not urgently) – May need to increase ECMO flow	No change given ECMO support is adequate	– No action needed, may choose to reintubate (not urgently) – May need to increase ECMO flow
Air trapped in the ECMO circuit	– Sudden stoppage of ECMO pump – Risk of air embolism	– Emergency: need to clamp ECMO circuit and plan for immediate de-airing of the circuit or replace it	– Sudden stoppage of ECMO pump – Risk of air embolism	– Emergency: need to clamp ECMO circuit and plan for immediate de-airing of the circuit or replace it
Circuit tubing rupture	– Sudden stoppage of ECMO pump – Circulatory collapse	–– Emergency: need to clamp ECMO circuit and plan for immediate reconnection at rupture site or replace it	– Sudden stoppage of ECMO pump – Circulatory collapse	– Emergency: need to clamp ECMO circuit and plan for immediate reconnection at rupture site or replace it
Hypoxemia	Low SpO_2 and PaO_2	– Increase ECMO flow if needed. May consider adding another venous cannula to augment venous return – Need to rule out recirculation: if present, lower ECMO flow, assure cannula position (CXR, echocardiography), and give IV fluid to increase RA size and CVP – Check oxygenator function by checking post-oxygenator gas[a]	Low SpO_2 and PaO_2	– Increase ECMO flow – Check oxygenator function by checking post-oxygenator gas[a]
Agitation	– Tachycardia – May interrupt ECMO flows and venous return by creating significant intrathoracic negative pressures when agitated	– Provide further sedation	– Tachycardia – May interrupt ECMO flows and venous return by creating significant intrathoracic negative pressures when agitated	– Provide further sedation
Seizures	– Tachycardia, altered mental status – Convulsive movements	– Long-term EEG – Anti-epileptic therapy	– Tachycardia, altered mental status – Convulsive movements – Decrease in SvO_2 saturation	– Long-term EEG – Anti-epileptic therapy

[a]Post-oxygenator gas: increasing the FiO_2 in the ECMO circuit flowmeter to 100%; then, 15 min later, obtain a blood gas sample from the port right after the oxygenator. A PaO_2 in the range of 300–500 mmHg indicates a properly functioning oxygenator

CDH and ECMO

CDH, which occurs in about 1:2500 live births (see Chap. 9), presents with pulmonary hypoplasia and a varying degree of pulmonary hypertension. After birth, severely affected neonates are hypoxic and hypercarbic and have pulmonary hypertension that requires targeted ventilation strategies to correct the hypoxia and hypercapnia using nitric oxide and pulmonary vasodilators to attenuate the pulmonary hypertension. ECMO may be required to correct or attenuate hypoxia, acidosis, and complications related to barotrauma and the inability to control the pulmonary vascular tone. ECMO corrects the inadequacy of ventilation while offering a period to rest the lung and offering further protection from barotrauma and a chance for the pulmonary hypertension to abate. Both VA and VV ECMO have been used to manage neonates effectively; cardiovascular support from VA ECMO may be needed especially if there are any questions regarding cardiac anomalies and function.

One of the most contentious issues is the timing of corrective surgery for CDH in neonates managed with ECMO: (1) after the ECMO run was complete or (2) during the ECMO run itself. Surgery performed during ECMO can be either early on after stabilization on ECMO or when the patient is deemed ready for ECMO decannulation. A CDH repair on ECMO ensures better management of the most common intraoperative concerns, which are intraoperative oxygenation and ventilation, especially during thoracoscopic procedures [74].

Reports are conflicting regarding which repair modality offers a better outcome. Each of these approaches holds benefits and risks. In a review of over 600 cases from the CDHSG registry [75] that were accumulated over 10 years, the outcomes from surgery either during or after ECMO were more favorable if the repair had occurred post-ECMO. The better outcomes were attributed to a reduced risk of bleeding as well as a bias toward patients who have improved more rapidly allowing for ECMO decannulation. However, their data failed to demonstrate whether the early/late timing of surgery during ECMO was superior.

The ability to wean off ECMO within 2 weeks may contribute significantly to the outcome vis-a-vis the timing of surgery [76]. If the patient was weaned off ECMO within 2 weeks, surgical correction post-ECMO was associated with a significantly better outcome and a significantly reduced risk of bleeding when compared with patients at that institution who were repaired on ECMO who were not able to be weaned off ECMO and had a "late" on ECMO CDH repair.

Early repair on ECMO offers the benefit of surgery before the anasarca becomes extensive and allows recovery from the physiologic insult while on ECMO, without prolonging the duration of ECMO. Early repair on ECMO demonstrated that the risk of bleeding was <10%, and the operative repair took less than 2 h with a 70% survival rate [77].

Anticoagulation during ECMO for CDH is an important aspect of the care especially if CDH repair is performed during the ECMO run. The inflammatory response triggered by ECMO also causes significant changes in the coagulation cascades resulting in the significant consumption of blood products. Optimization of the AT activity is important for effective heparin anticoagulation in ECMO patients. A review of AT use (target activity >65%) in CDH ECMO patients when compared with the institutions' historical control demonstrated that when AT was maintained, the use of FFP, packed red cells, and platelets were significantly reduced in the first 3 days of ECMO [78]. The use of large volumes of blood products may adversely affect lung mechanics and delay recovery.

Pulmonary hypoplasia is the underlying cause of hypoxia and hypercapnia that results in the need for ECMO support. Perfluorocarbons (PFC) have been used to support alveolar maturation. In a prospective randomized study of CDH patients on ECMO, the use of PFC was evaluated for lung growth using L1 vertebral body size for comparison [79]. After the PFC was instilled into the tracheal tube until a meniscus could be seen and CPAP was maintained at 8 cm H_2O, the PFC was "topped off" as needed during the ECMO run to maintain a visible meniscus in the tracheal tube. The size of the left (affected) lung increased 130% during the use of PFC, without side effects or other complications. However, the lung growth in the non-PFC group was not reported, and the mortality was similar in both groups.

In severe CDH, every ventilator strategy is capable of causing barotrauma before ECMO support can be initiated, resulting in pneumothoraces and further damage of the lung parenchyma. The ex utero intrapartum treatment (EXIT) procedure has been used for specific neonatal conditions. For neonates in whom ECMO is considered 100% likely, then an EXIT to ECMO management strategy provides maximal protection for the hypoplastic lung. In a small study that reported the EXIT to ECMO strategy for CDH patients with prenatal lung volumes <15% predicted [80], there were no demonstrable benefits to using the EXIT procedure in terms of the mortality, complications, or duration of ECMO. The EXIT procedure is no longer offered as an option now at that institution.

Trends in Neonatal ECMO: The Future

ECMO continues to be an important supportive therapy for neonates with severe cardiorespiratory failure that is unresponsive to conventional therapies. Over the last 3 decades, the use of neonatal respiratory ECMO has decreased because of advances in neonatal medicine including surfactant use, HFOV, and inhaled nitric oxide. At the same time, the use of ECMO has increased for patients with more complex diagnoses, and the duration of ECMO support has

also increased. A standardized evidence-based approach to managing anticoagulation in neonatal ECMO has not been forthcoming. Nonetheless, the use of DTIs is an emerging alternative to UFH, but more evidence and experience are needed before these strategies become widely adopted.

Pulmonary diseases continue to be the principal diagnoses for the use of neonatal ECMO support, with an overall 73% survival rate and up to one-third of cases due to CDH.

The future is full of potential advances in knowledge, technology, and expertise that will push neonatal ECMO boundaries toward younger and younger neonates and increasingly complex patients, with less ECMO-related complications and improved overall survival and quality of life.

Conclusion

ECMO is a life-saving support strategy that is offered to increasingly complex neonatal patients with cardiorespiratory failure that is unresponsive to conventional therapies. Bleeding and thrombosis are the most common complications. Major advances in ECMO care have resulted in a safer practice with decreasing trends of mechanical complications. CDH remains a major challenge in neonatal ECMO with relatively high mortality throughout the years. Initiating ECMO before the onset of severe hypoxemia, hypotension, and acidosis may improve outcomes and reduce mortality and long-term morbidity.

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Anesthesia Outside the Operating Room

13

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Neonates Are Not Small Children

In the same way children are not just small adults, neonates (especially premature neonates) are not small children. There are a number of unique physiological features in term and premature neonates that hold great importance to the anesthesiologist. Some of these features are shown in Fig. 13.1 and described below:

1. *Oxygen toxicity*: Human fetuses are hypoxemic with PO_2 values ranging between 20 and 32 mmHg. The antioxidant mechanisms are not well developed in neonates [1], and premature infants are even more susceptible to oxygen toxicity after exposure to excessive levels of oxygen [2]. The associations between oxygen exposure and retinopathy of prematurity (ROP) and bronchopulmonary dysplasia (BPD) are well established [3–7]. Several animal and human studies have also reported increased pulmonary arterial contractility [8], biochemical oxidative stress [9], and increased risk of cancer [10] after even brief exposure to 100% oxygen in the delivery room at birth. In the past, anesthesiologists routinely used 100% oxygen to ventilate the lungs of neonates with during surgery to avoid hypoxia or due to a lack of the availability of air in the OR. Increased awareness of oxygen toxicity has led to changes in this practice. In the OR, all neonates undergoing emergent surgery with a rapid sequence induction (RSI) to secure the airway are still preoxygenated for several minutes to prevent desaturation while the airway is secured, although most neonates do not tolerate a face mask without objection. This practice continues today. A 2008 survey of 247 anesthetists in the United Kingdom reported that 52% of respondents delivered <40% oxygen during neonatal anesthesia and < 16% delivered >40% oxygen [11]. Few anesthesiologists administered 100% oxygen to neonates and premature infants [11]. However, 10% of the respondents suggested that they do not make a conscious effort to avoid 100% oxygen during neonatal anesthesia even though this concentration is associated with pulmonary atelectasis. The potential risks of desaturation during anesthesia and concern over the need for a margin of safety in light of the evidence that the incidence of desaturation including severe desaturation (<80%) increases with decreasing age [12] have led to the use of 30–40% oxygen during neonatal anesthesia (in the absence of significant lung disease) to maintain a target preductal oxygen saturation (SaO_2) of ~90% (see Chaps. 2 and 17). The pulse oximeter should be sited on the right hand (preductal) to display the SaO_2. SaO_2 of 99–100% are often associated with supraphysiological PaO_2 and potential toxicity to the retina and lungs in neonates and, in particular, in very low birth weight (VLBW) infants. SaO_2 of 85–89% have been associated with an increased mortality when compared with 91–95% in infants <28 weeks' gestation at birth, although this notion remains contentious and unresolved (see Chaps. 2 and 17). SaO_2 should be closely monitored during mechanical ventilation of both premature and full-term neonates under anesthesia with a target SaO_2 range set to 90–93%, to limit ROP and lung disease while avoiding a possible increase in mortality [5–7].
2. Similarly, the use of 100% oxygen for transport from the NICU to the OR is also contentious. The use of 100% oxygen delays the time to serious desaturation in both infants [13] and critically ill patients during transport [14]. This allows more time for corrective action before

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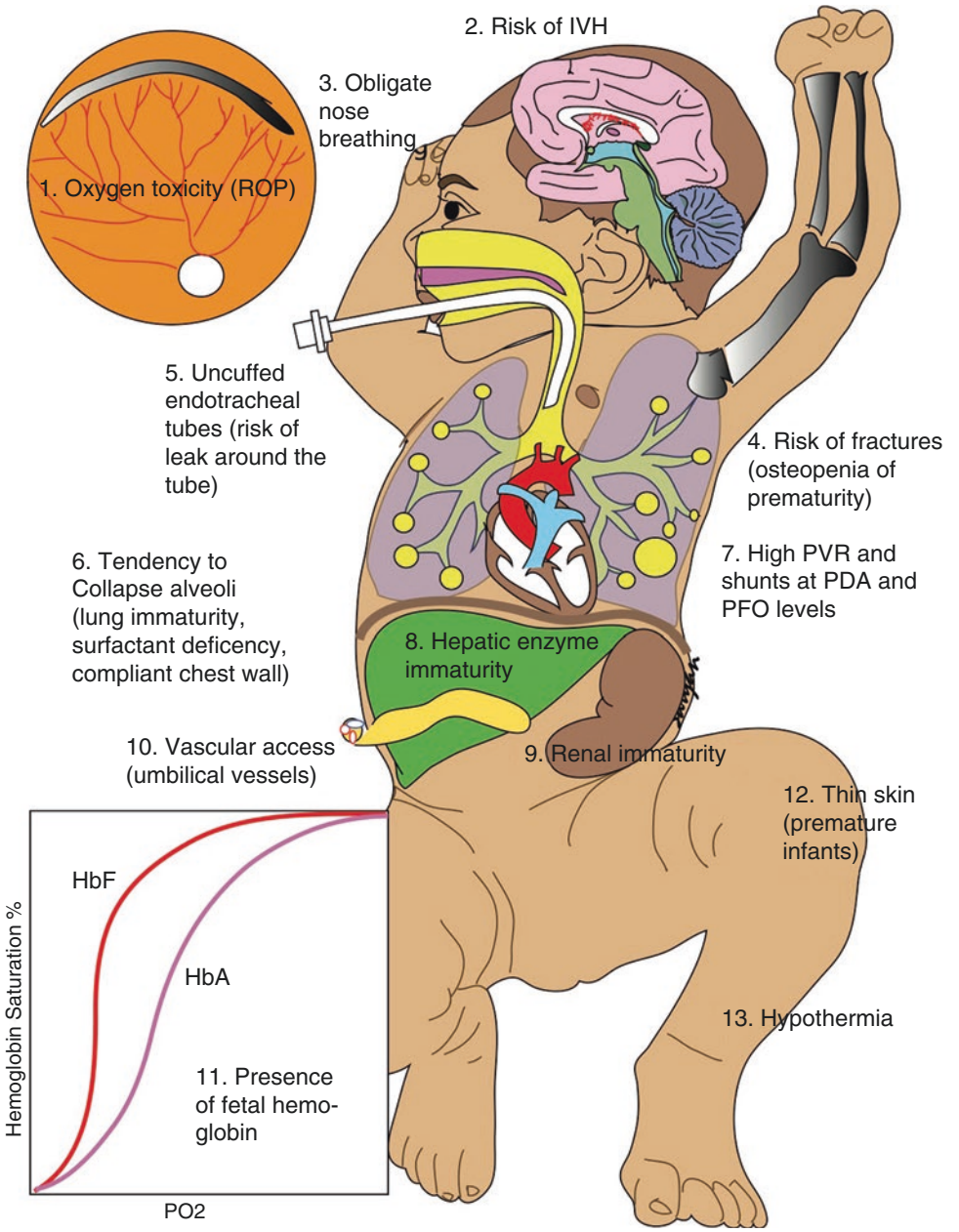

Fig. 13.1 Physiologic factors in the full-term and premature infants that can influence their management during anesthesia and surgery. See text for details

cardiac and neurologic sequelae from hypoxia may occur. The practice of using 100% oxygen for high-risk procedures balances the potential of a possible long-term risk of ROP and lung disease against the immediate potentially lifesaving benefits of delayed desaturation and cardiac arrest.

3. Lung development continues during fetal life with limited surfactant production until almost 34 weeks' gestation [15]. The combination of a lack of surfactant and a compliant chest wall increases the risk that the small bronchioles will collapse during expiration. Positive end-expiratory pressure (PEEP) is crucial during ventilation in premature infants. Furthermore, if BPD is present, airway resistance is increased leading to an increased risk of air trapping. The use of appropriate PEEP, low rates, and prolonged expiratory times may be necessary to optimize ventilation (see Chap. 6).
4. Respiratory control is immature in premature infants resulting in episodes of apnea and bradycardia. The risk of postoperative apnea (of prematurity) increases with infants of younger gestational and/or postconceptional age and anemia [16].
5. Premature and full-term neonates are considered obligate nose breathers, although they are capable of mouth breathing during nasal occlusion [17]. The shift to mouth breathing in response to nasal occlusion becomes more automatic with advancing postconceptional age [18]. Nonetheless, infants with choanal stenosis and atresia

and some craniofacial anomalies (e.g., Pierre Robin sequence, Crouzon syndrome) remain at risk for apnea. It is important to suction the nares and ensure the patency of the nasal passages before extubating the trachea in these infants.

6. Uncuffed tracheal tubes (TTs) have been the standard for premature and term neonates until recently. Issues associated with the use of uncuffed TTs during anesthesia include difficulties in maintaining targeted tidal volumes during mechanical ventilation (particularly in infants with poorly compliant lungs), multiple tracheal intubations to achieve a properly sized tube, and expiratory gas leak and OR pollution [19, 20]. Two manufacturers presently supply small-diameter cuffed TTs: the Lo-Pro/Lo-Contour 3.0 mm internal diameter TT (Mallinckrodt© USA) and the 3.0 mm Microcuff® TT (Kimberly Clark, USA). These TTs have similar outer diameters as the comparable uncuffed TTs, although the latter tubes are uniquely designed to include an elliptical-shaped, more caudally placed, thin-walled cuff without a Murphy eye. Few studies have documented the safety and long-term use of these TTs in premature and full-term neonates [21]. A recent report cited three cases of stridor in young infants whose weights were less than those recommended for the 3.0 mm Microcuff® TT, 3 kg, suggesting that even high-compliance cuffed TTs may cause stridor and possible airway trauma in premature neonates [22]. Conflicting retrospective data have been reported: in one study of 324 neonates, post-extubation stridor occurred in 17.2% of those who had the Microcuff® tube (compared with 7.5% with uncuffed tubes) which logistic regression concluded that stridor after the cuffed tubes occurred with an adjusted odds ratio of 9.27 [23], whereas in a second retrospective study of 46 neonates with Microcuff® or uncuffed tubes, complications including stridor after extubation were similar [24]. The use of cuffed TTs in premature and full-term neonates <3 kg should only be undertaken with great caution, pending further large-scale studies [25] (see Chap. 5).
7. Premature and term infants may have increased PVR. When PVR increases as in the presence of hypoxia or acidosis, right-to-left shunting of blood at the patent foramen ovale (PFO) or patent ductus arteriosus (PDA) may occur, resulting in cyanosis [26, 27]. Since the pCO_2 may directly increase the PVR, one strategy to reduce the PVR is to reduce the pCO_2. However, hypocarbia from overventilation decreases cerebral perfusion and may lead to periventricular leukomalacia (PVL) in premature infants [28].
8. Intraventricular hemorrhage (IVH) is common in extremely low birth weight (ELBW) premature infants [29]. Friable vasculature in the subependymal region of the lateral ventricles is prominent during early gestation and involutes with advancing gestational age. Several risk factors increase the risk of IVH including wide fluctuations in $PaCO_2$ or hypercapnia, rapid infusion of fluids and sodium bicarbonate, and increases in intrathoracic pressure (e.g., as a result of pneumothorax) [30]. Studies in ELBW infants (<1000 g at birth) suggest that wide fluctuation in $PaCO_2$ (i.e., difference between maximum and minimum $pCO_2 > 42$ mmHg) during the first 4 days of life is an important risk factor for IVH [31]. Wide swings in monitored variables should be avoided during anesthesia as well [32], although this presents a great challenge in infants with BPD.
9. Immaturity of the hepatic enzyme systems increases the neonate's risk for toxicity from medications [33]. Neonates receiving parenteral alimentation for prolonged periods are at risk for cholestatic liver disease [34] resulting in further compromise to hepatic function.
10. Fetal accretion rates for calcium and phosphorus are large. Many growing premature infants cannot maintain similar bone mineralization after birth because of low calcium and phosphorus absorption from parenteral and enteral nutrition [35]. In addition, many extremely premature infants receive medications such as diuretics, methylxanthines, and steroids that interfere with calcium metabolism. These infants may develop osteopenia of prematurity [36] and are susceptible to pathological fractures. The risk of osteopenia and fractures increases as gestational age decreases. These fractures can occur during routine limb manipulations such as placement of an intravenous catheter. Anesthesiologists should be aware of the existence of previous pathological fractures and the present serum alkaline phosphatase levels [35, 37]. Alkaline phosphatase levels >750 IU/L may be associated with radiological features of osteopenia in some premature infants. In the 1980s, the incidence of osteopenia was 50% in premature infants (<1000 g birth weight). Fractures were detected in as many as 24% of these infants. With better nutrition, the incidence of osteopenia and fractures has decreased in recent years [35], although this problem persists.
11. Glomerular filtration rate (GFR) is reduced in premature and term neonates but improves postnatally reaching adult rates by 1–2 years of age [38]. The use of nephrotoxic medications such as indomethacin and vancomycin may compromise renal function in some cases requiring blood sampling to determine concentrations at increased intervals between doses.
12. During the first few postnatal days, umbilical vessels provide arterial and venous access to sick neonates. Anesthesiologists should be familiar with the location of these lines (see below).

13. Term infants at birth have approximately 70% fetal hemoglobin (HbF). HbF has increased affinity for oxygen resulting in a greater SaO_2 compared with adult hemoglobin (HbA). For example, a pulse oximeter reading of 90% is associated with a PaO_2 close to 60 mmHg with HbA but maybe as low as 50 mmHg in premature infants with increased levels of HbF. Some infants receive multiple packed RBC transfusions, thereby increasing the HbA content. The oxygen dissociation curve in such infants with multiple blood transfusions resembles that of adults resulting in a reduced SaO_2 (e.g., PaO_2 of 50 mmHg will result in an SaO_2 of 85% in a baby that has received multiple transfusions).
14. Premature infants have thin permeable skin and are prone to increased heat and water loss by evaporation during the first few days of life (see Chap. 8). This thin fragile skin is vulnerable to accidental loss from peeling adhesive tape.
15. The ratio of surface area to body weight in neonates exceeds that in adults. As a consequence, the neonate is at increased risk for heat loss by radiation (39%), convection (34%), evaporation (24%), and conduction (3%) [39] (see Fig. 8.6).

During surgery, appropriate measures to maintain thermal homeostasis must be used including a servo-controlled or thermal-neutral incubator during transport to the suite in which the procedure/investigation takes place, increasing the OR temperature before the neonate arrives, using an overhead heat lamp, a thermal mattress, and a forced-air warmer. Some or all of these devices may not be MRI compatible and cannot be used in that environment. The skin should remain dry, and contact with wet linens should be avoided to prevent heat loss. Direct contact with the heating sources must also be avoided to minimize the risk of skin injury.

Benefits of Performing Surgery in the NICU

The most common reason for performing surgery in the NICU is to avoid comorbidities that may occur during transport of the critically ill neonate to another unit, such as the OR. There are several potential risks associated with transporting these infants (Table 13.1) [40]. The transport may require a change in the mode of ventilation [41]. Transporting a neonate whose lungs are ventilated with a high-frequency oscillatory ventilator (HFOV) or high-frequency jet ventilator (HFJV) is difficult and very challenging. Often, the lungs must be ventilated manually during transport and HFOV reinstituted only upon arrival in the OR. The transport incubator should be designed to maintain the neonate's temperature [42]. The neonate requires four transfers [43] during the trip to the OR (NICU bed to the transport incubator, incubator to the OR table, OR table back to the transport incubator, and lastly from the incubator back to the NICU bed). The risks are increased with the distance to be traveled and the need to use an elevator [42]. In a report of neonatal surgical practices from the United Kingdom in 2005 [44], more than one-third of the transports to the OR involve transfer to a separate building from the NICU, whereas only 3% of the responders provide anesthesia for surgical procedures in the NICU. Furthermore, the neonate is difficult to observe during the transport. Monitors during the transport often suffer from interference or movement artifact rendering the measurements unreliable, and the frequency of false alarms may mask true critical events. This, along with the fact that it is more difficult to clinically assess the neonate in the closed incubator, may cause a delay in the diagnosis and management of complications such as hypoxia, bleeding, pneumothorax, and cardiac arrest.

Table 13.1 Risks of transporting neonate

Disrupting of stable ventilation parameters
Loss of the airway or movement of the endotracheal tube
Loss of IV or central line access and interruption of infusions
Hypothermia
Requirement for four transfer episodes
Distance to operating room
Cardiovascular instability
The postoperative patient is usually more fragile
Difficulty in examining the neonate during transport
Incompatibility of monitoring systems between the NICU and the OR

When transporting the neonate, ventilation is usually manually performed. If a self-inflating resuscitation bag system or T-piece (Mapleson C or F) resuscitator is used, accidental extubation may not be detected as the change in compliance may be difficult to detect [45] and the resuscitation bag automatically reinflates even with a large leak. A Mapleson type C anesthesia circuit will not reinflate fully without adjustment of the expiratory valve, and the change in compliance due to esophageal, pharyngeal TT placement will be more easily felt. Capnography may facilitate early detection of extubation, but it is infrequently included in the transport monitors.

Hypothermia is more common after a procedure in the OR than in the NICU [46, 47]. In a comparison of 80 infants undergoing laparotomy or diaphragmatic hernia repair, the core temperature decreased by 2.2 °C in those who underwent surgery in the OR compared with 0.6 °C in those who underwent surgery in the NICU [48]. Extreme hypothermia (30 °C) has also been reported in neonates after surgery in the OR [41]. The risk of extreme hypothermia (<33 °C) is more com-

mon in VLBW neonates <1500 g. Strategies to reduce perioperative hypothermia during transport to and from the OR and during surgery have been the focus of quality improvement projects in many institutions with salutary results [49].

Interestingly, there are also reports of hyperthermia (>37.5 °C) in neonates who underwent surgery in the OR [26, 49]. Hyperthermia in the perioperative period should be eschewed. Hyperthermia in the immediate postnatal period in infants with hypoxic–ischemic encephalopathy has been associated with worse outcomes [50]. Perioperative hyperthermia and transfusions in healthy neonates and infants <6 months are associated with similar increases in the odds ratios for surgical site infections (~3.7) in the first 30 postoperative days [51].

Patient Indications for Surgery in the NICU

There are several patient indications for performing surgery in the NICU (Table 13.2). Neonates who are too unstable to transfer either within the hospital or between hospitals and those in whom the risk of mortality is very high with or without the operative procedure (ASA class 5) are good candidates to undergo surgery in the NICU. Performing surgery in VLBW neonates <1500 g in the NICU has resulted in more stable clinical situation with less disruption of physiologic parameters [41]. Transporting neonates who require high-frequency (HFJV or HFOV) ventilation is difficult, requiring the presence of a respiratory therapist and neonatologist in the OR for the duration of the surgery to assist with the ventilation management as well as the transport back to the NICU. However, there is insufficient evidence to suggest that specialized neonatal transport teams impact perioperative morbidity and mortality [52]. Furthermore, the anesthesia workstation ventilator may be incapable of ventilating the neonate's lungs with the same mode and parameters as were used with the NICU ventilator. In the latter instances, respiratory therapy could provide an appropriate ventilator for the neonate in the OR. Additionally, when emergent surgery is required and the OR is fully occupied, the surgery can be performed in the NICU without delay, assuming OR personnel is available.

Table 13.2 Indications for neonatal surgery in the NICU

Too unstable for transfer
Weight <1000 g or <1500 g
High-frequency oscillatory ventilation
Jet ventilation
Inhaled nitric oxide
Complex conventional ventilatory requirements
Surgical team willing to do "out-of-OR surgery"
Emergency procedure and delay in the OR

Logistics of Performing Surgery in the NICU

In order to provide anesthesia and perform operative procedures in the NICU, several logistic considerations need to be appreciated (Table 13.3). Consent must be obtained for the anesthetic and surgery from the parents or guardians. A thorough discussion of risks and benefits of anesthesia and surgery in very unstable infants must be completed in advance, in order to prepare for all possible options that may ensue including the need for changes in ventilation, blood transfusion, and cardiopulmonary resuscitation. Although parents may be present at the infant's bedside during routine care, we do not allow parents to be present during surgery in the NICU.

The surgeon and surgical team require a complete sterile surgical equipment tray, gowns, gloves, and masks. Appropriate surgical lighting must also be available, including portable overhead lights as well as surgical optical headlights and light sources [53]. Appropriate suction and cautery equipment must also be available. A full array of surgical instruments must be immediately available in the NICU in the event additional instruments are unexpectedly required urgently.

The anesthesiologist requires access to pharmacological, airway, and fluid supplies. An anesthetic workstation is usually neither available in the NICU nor required as inhalational anesthetics are infrequently used for several reasons including the absence of waste gas scavenging in the NICU. As a result, anesthesia in the NICU is usually a total intravenous technique that consists of intermittent boluses of opioids and muscle relaxants. Infusion pumps are generally not used unless inotropes are required. Most monitors that are required are present in the NICU, although they may be difficult to access. One monitor that historically has been absent in the NICU is a capnogram. Many NICUs are now routinely using end-tidal CO_2 monitors, especially in VLBW infants, although modern transcutaneous CO_2 ($TCCO_2$) monitoring responds more rapidly and is more reliable than was reported previously (see below). If a capnogram is not present, a portable capnogram may be brought from the OR, unless the neonate is ventilated with HFO, in which case the capnogram will be of limited value. A fluid warming device

Table 13.3 Logistics of performing operative procedure in the NICU

Availability of surgical equipment and lighting
Availability of anesthesia equipment
Location for operative procedure
Consideration for other NICU patients
Infection control
Communication
Team concept

is recommended if large volumes of fluids or blood are required. Emergency equipment should also be available in the NICU including a resuscitation cart.

$TCCO_2$ is a commonly used monitor in the NICU, whereas in the OR end-tidal CO_2 monitoring ($ETCO_2$) is the standard monitor to assess the adequacy of ventilation. In neonates, $ETCO_2$ may not be accurate due to the large sampling flow rates, rapid respiratory rates, and circuit dead space. Moreover, when HFOV or jet ventilation is used in the NICU, $ETCO_2$ is simply impossible. In a comparison of $ETCO_2$ and $TCCO_2$ in neonates and infants <10 kg to the venous CO_2 as the gold standard, a Bland–Altman analysis demonstrated that $ETCO_2$ underestimated $PvCO_2$ [54, 55]. This underestimation was much more apparent in NICU neonates ($ETCO_2$ about −30 mmHg $PvCO_2$) than in healthy OR neonates ($ETCO_2$ about −10 mmHg $PvCO_2$). This significant bias in the NICU may be due to the increased ventilation settings required in these critically ill patients. These studies suggested that the $TCCO_2$ may be a more accurate assessment of the respiratory status of critically ill neonates and it may be helpful even during surgery involving conventional ventilation modes. However, if the $ETCO_2$ is available, it should be used as it will detect events such as accidental extubation or tube occlusion episodes more rapidly than $TCCO_2$ [56]. If $TCCO_2$ monitoring is used, attention should be paid to frequently calibrate the sensors and to carefully monitor the skin site for burns. The sensors should be repositioned in extremely preterm infants as their fragile skin is more likely to break down than that of older neonates.

When surgery is performed in the NICU, it occurs at the neonate's bedside location. Before surgery, all visitors and nonessential staff are cleared from the procedure area before the OR staff arrive. This should limit the risk of airborne contamination and microbial shedding resulting in infections. The use of barriers will also discourage inadvertent access to the operative procedure by unauthorized persons. Many new neonatal units have single-patient room design to address these concerns. Space constraint may necessitate transfer to a larger room. Some NICUs have a fully equipped procedure room with a high airflow exchange or a "twin room" with a larger area that may be used in the NICU unit. In this case, the infant is transferred to the procedure room, which is usually a short distance away, while being accompanied by the NICU support staff.

A study compared outcomes for both PDA and congenital diaphragmatic hernia (CDH) patients operated in a dedicated surgical procedure room within the NICU and the OR [47, 57]. The main benefits for performing surgery in the NICU were a reduction in waiting time for procedure start, a reduced postoperative FiO_2, and a reduction in the frequency of hypothermia. Surgical-related complications were similar. Start time efficiency was improved aided by not having to transfer the neonate to the OR. The ventilation status was improved despite the fact the neonatologist was responsible for ventilation management in both locations. The incidence of hypothermia was reduced fivefold. Also, routine NICU care for other patients as well as family access to the patient's room was unaffected. After the operative procedure, the neonates remained in the NICU procedure room until they were stable, managed by their regular bedside nurse and physician team, before being transferred back to the regular bed location. This arrangement may offer the best of both worlds but does require significant capital and operational investment.

Good communication among the NICU and the OR staff, the surgical team, and the anesthesiologist is very important. Moreover, establishing a close liaison with the NICU bedside nurse before anesthesia and surgery commence is very helpful to ensure that the latest laboratory values are available and within acceptable limits, that intravenous and intra-arterial accesses are available at a distance from the neonate, and that blood products are available if deemed necessary. Since anesthesiologists have a limited knowledge of the layout of the NICU, it is imperative that the bedside nurse is available to provide syringes, needles, and other supplies during the surgery.

For sites where anesthesia does not customarily provide general anesthesia, we always include a portable anesthesia equipment cart that is stocked with a full complement of airway supplies, noncontrolled medications, and IV equipment that may be needed during the procedure. Securing the airway with a TT before the surgery whether in the NICU or OR is mandatory. In most instances, direct laryngoscopy with the Miller 0 or 1 blade is effective [58, 59], although backup equipment in the form of a videolaryngoscope is essential should a difficult airway be encountered. Both the C-MAC Miller and the Glidescope video laryngoscopes have been used successfully in neonates [60–62]. The C-MAC video laryngoscope with a Miller 0 blade has recently been shown to be safe and effective for tracheal intubation in both premature and ex-premature infants in a small sample [63]. Apart from its use to improve proctoring and teaching, there is no evidence that videolaryngoscopy is superior to direct laryngoscopy in trainees performing tracheal intubation in neonates [64]. Access to such equipment should be readily available for both anticipated and unanticipated airway situations [65, 66].

Similarly, the presence of the neonatologist at the bedside is extremely important in order to ensure that changes in management strategies of the neonate, such as ventilation changes, are undertaken with a thorough understanding of the child's preexisting conditions. A cooperative environment will increase the efficiency and safety of the anesthetic and surgery. An efficient and organized surgical service for the NICU minimizes disruption of the care the nurses must provide to the other infants in the room and minimizes the time that family members of other neonates in the room are barred from visiting their infants.

The recent COVID-19 pandemic demonstrated additional concerns with operating and providing anesthesia outside the

OR. Aerosol-generating procedures with intubation and other respiratory support modalities (high-flow nasal oxygen) increase the risk of transmission. Prior testing of the neonate for SARS CoV-2, minimizing personnel in the NICU room, wearing appropriate PPE, and having adequate airflow are key to reducing risk of SARS CoV-2 transmission to healthcare workers [67].

Vascular Access

Establishing adequate vascular access in neonates may be challenging. This is particularly challenging in ELBW infants (<1000 g birth weight). In addition to peripheral venous access, some neonates may have umbilical lines and percutaneous peripherally inserted central catheter (PICC) lines. Anesthesiologists should be comfortable using these access lines and should be capable of inserting lines in emergency situations. A brief review of umbilical venous and arterial lines and PICC lines is given below:

1. *Umbilical venous catheter*: The umbilical vein is large and easily accessible in neonates. Many infants in the NICU have an indwelling umbilical venous line for the first 5–7 days of life. It is important to document the exact location of the tip of the umbilical venous catheter on a recent X-ray before using it during anesthesia. The optimal location of the catheter tip should be in the inferior vena cava at or just above the level of the diaphragm (Fig. 13.2). If the catheter tip is caudal (in hepatic veins), hepatic necrosis can occur in response to the infusion of hypertonic or vasospastic solution into the liver tissue [68]. If the catheter tip is too rostral, it may be located in the right atrium, superior vena cava, foramen ovale, left atrium, pulmonary veins (Fig. 13.3), right ventricle, or pulmonary artery. These locations may be associated with complications such as pericardial effusion, pleural effusion, and cardiac arrhythmias. Umbilical venous catheters are usually 5 Fr in diameter (occasionally 8 Fr in large term infants), consisting of either single-lumen or double-lumen catheters. These cath-

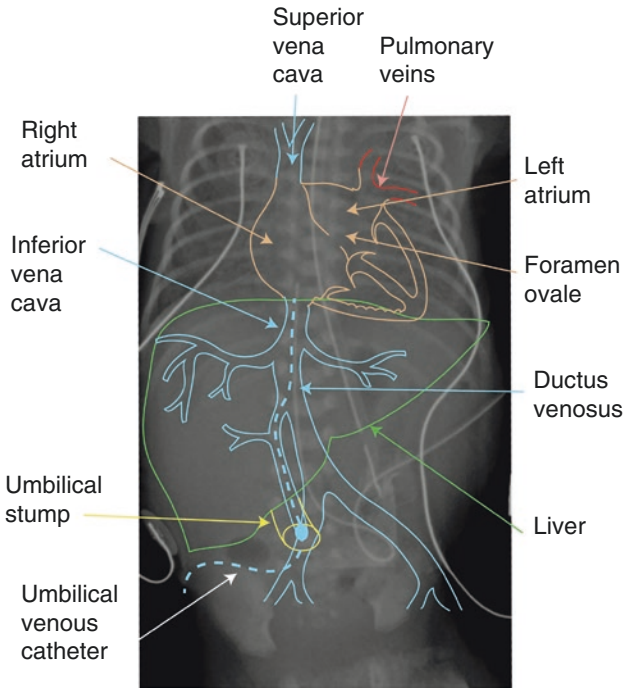

Fig. 13.2 Optimal position of the umbilical venous line. The tip of the umbilical venous catheter should be located in the inferior vena cava just above the level of the diaphragm

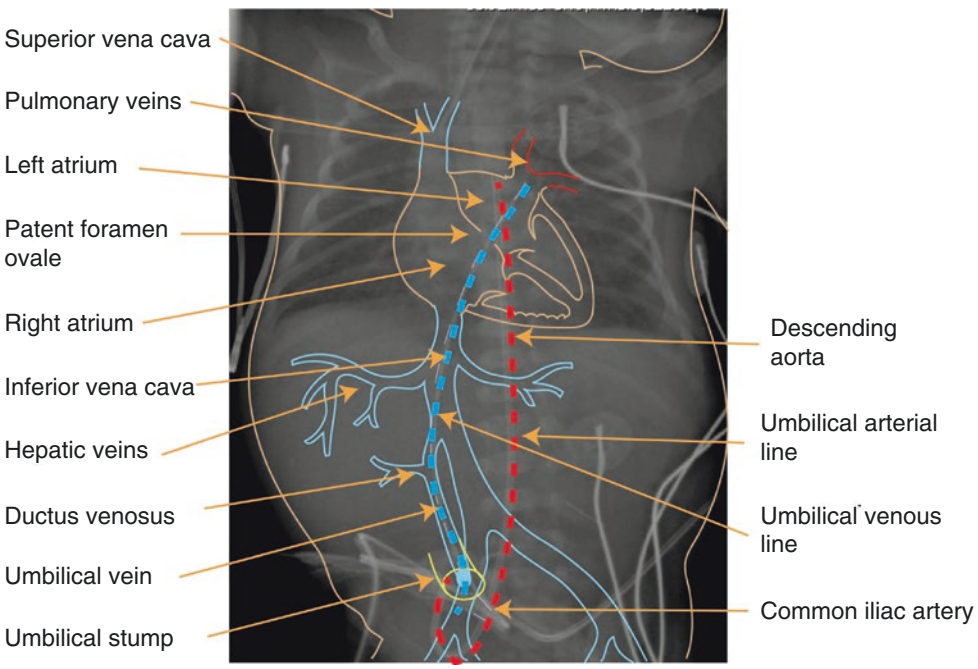

Fig. 13.3 Umbilical venous catheter advanced into the right atrium, PFO, left atrium, and pulmonary veins (shown by *dashed blue lines*). This is an inappropriate location for an umbilical venous catheter. The umbilical arterial catheter is shown in red dashed lines

eters should not be left open to atmosphere (because of the risk of an air embolus) [68]. For emergency vascular access, vital infusions (not hypertonic solutions) may be administered slowly through an umbilical venous catheter placed in the umbilical vein (usually 2–4 cm below the skin) [68] and checking for blood return, prior to use. The umbilical venous catheters traverse the falciparum ligament and are usually removed before laparotomy.

2. *Umbilical arterial catheter*: An umbilical arterial catheter is often placed in a sick neonate to monitor blood pressure and to sample blood (especially arterial blood gas samples). The catheter is usually a 3.5 Fr or a 5 Fr single-lumen catheter placed in the umbilical artery and advanced into the aorta. The catheter tip is usually located either high (at the level of thoracic vertebrae 6–9) or low (at the level of lumbar vertebrae 3–4). Locating the catheter tip between thoracic vertebra 10 and lumbar vertebra 2 is best avoided because this region includes the origins of the celiac, mesenteric, and renal arteries (Fig. 13.4). If the catheter tip is located above thoracic vertebra 6, there

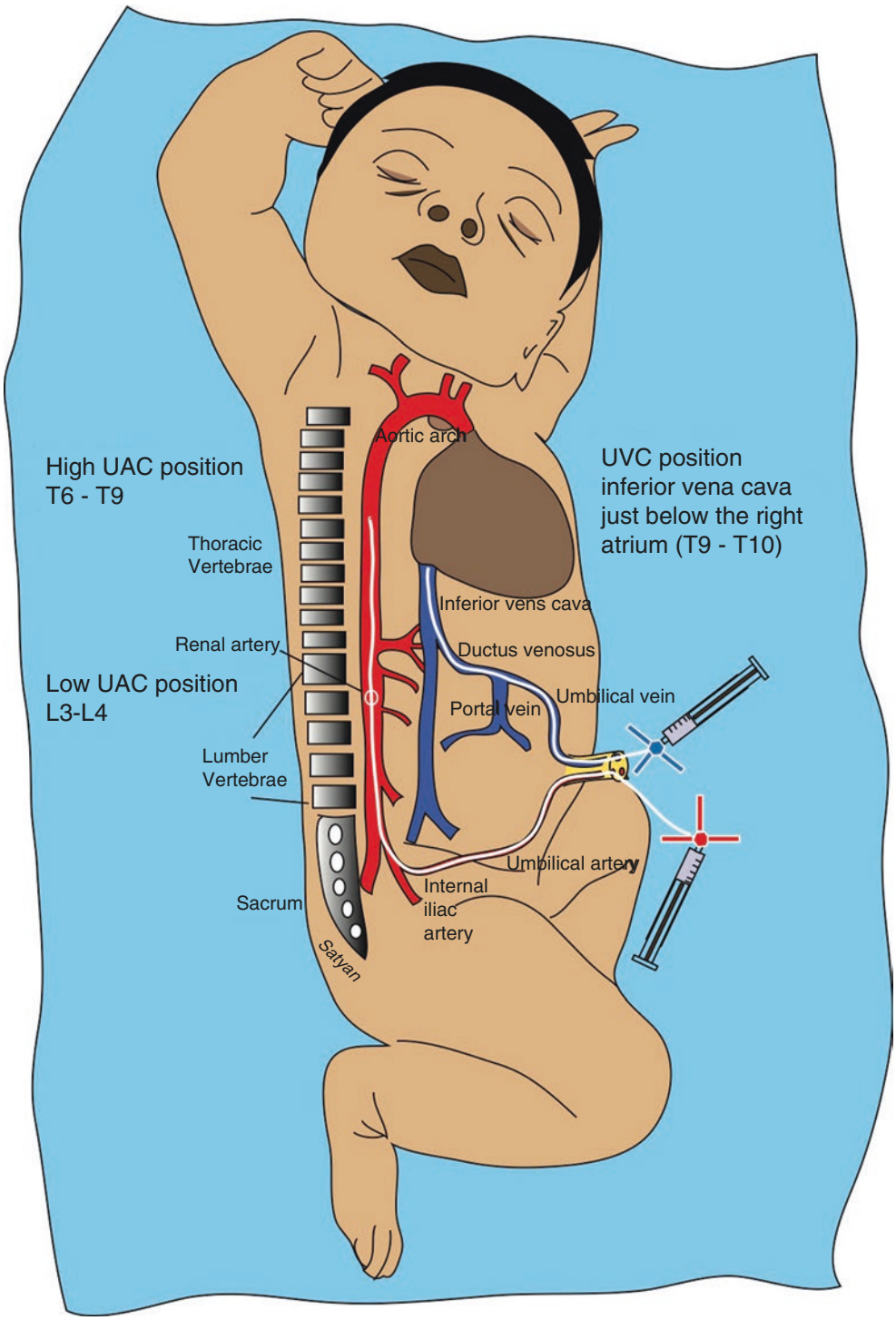

Fig. 13.4 Appropriate locations of the umbilical venous and arterial catheters from a lateral view. The umbilical venous catheter traverses the umbilical and portal veins and enters the inferior vena cava through the ductus venosus. The optimal location of the tip is in the inferior vena cava just below the right atrium. The umbilical arterial catheter is advanced through the umbilical, internal iliac, and common iliac arteries and advanced into the aorta. The celiac axis, superior and inferior mesenteric arteries, and renal arteries arise from the abdominal aorta at the level of thoracic vertebra T12 to lumbar vertebra L3. The umbilical arterial catheter can be positioned below this region (low line L3–L4) or above this region (T6–9, as shown in this figure)

is a risk of embolization to the carotid and subclavian arteries. Umbilical arterial catheters can also be used to deliver parenteral fluids, although vasospastic agents such as dopamine are best avoided. If there is evidence of vascular compromise (pallor in the lower limbs and buttocks), the umbilical line should be removed immediately. In neonates in whom abdominal emergencies such as spontaneous intestinal perforation (SIP) are developing, the umbilical arterial catheter should be removed before surgery. To remove an umbilical arterial catheter, the catheter should be withdrawn slowly until approximately 5 cm remains in the vessel and then tightened using an umbilical tie around the base of the umbilical cord (and not on the skin). The remainder of the catheter should be pulled out of the vessel at a slow rate of 1 cm/min (to allow vasospasm of umbilical artery). If bleeding occurs once the catheter has been removed, lateral pressure should be applied to the cord by compressing it between the thumb and first finger [69].

3. *Peripheral arterial cannulation*: The most peripheral artery with good collateral flow, with low infectious risk, and that is large enough to measure systemic blood pressure should be selected for cannulation [70]. Ongoing bacteremia and fungal infections are relative contraindications to arterial cannulation because of the risk of colonization of the catheter. Common sites for peripheral cannulation include the radial, ulnar, dorsalis pedis, and posterior tibial arteries, with the right radial artery selected most commonly in one retrospective review of infants <5 kg [71]. Evidence for collateral flow must be checked before cannulation. This can be done by using a modified Allen test or by Doppler ultrasound [72]. Transillumination of the wrist is helpful in identifying the location of radial, ulnar, dorsalis pedis, and posterior tibial arteries. Care should be taken not to injure the ulnar nerve during ulnar arterial cannulation as it runs along the medial side of the artery. Sedation and analgesia with fentanyl are usually provided before arterial cannulation. Some also infiltrate the site before arterial cannulation with 0.5 mL of lidocaine. After aseptic precautions are followed, an Angiocath is inserted into the artery by direct puncture and advanced at a 10–15° angle to the skin with the bevel facing down [73]. When blood appears in the stylet, the cannula is advanced off the stylet and into the artery. Alternately, the needle stylet may be inserted at a 30–40° angle to the skin with the bevel facing up through the artery. The stylet is removed, and the cannula is withdrawn slowly until pulsatile arterial flow is established. The cannula is then advanced into the lumen of the artery [70]. A third technique is to employ a guidewire that is threaded into the cannula upon accessing the artery. This technique increases the rate of successful cannulation compared with direct palpation [74]. With the introduction of ultrasound guidance, the success rate for first-pass cannulation of the radial artery increased with the use of the ultrasound compared with direct palpation [75]. Most recently, cannulation of the radial artery in neonates using ultrasound in the short-axis view was compared with direct palpation [76]. Ultrasound resulted in a first attempt greater success rate as well as faster insertion time and fewer complications than the direct palpation approach. The introduction of new techniques for vascular cannulation in neonates including the use of a guidewire and ultrasound has increased the success rate for radial artery cannulation and reduced the complication rates.

   The site of insertion should be covered with a transparent semipermeable dressing to facilitate early detection of bleeding at the site. All fingers/toes should be clearly visible to monitor for signs of vascular insufficiency. Complications of peripheral arterial cannulation in neonates include thrombosis, vasospasm, infection, hematoma, damage to peripheral nerves, and air embolism [71, 77–79].

4. *Central venous catheterization*: Placing a PICC is a common procedure in the NICU to establish long-term central venous access in neonates. PICC lines are 1.1–5 Fr catheters of varying lengths, with the smallest single-lumen size being 1.1 Fr and the smallest double lumen being 2 Fr. In general, 1.1–2 Fr catheters are used in infants <2500 g and 1.9–3 Fr in those >2500 g. The PICC tip should be located in the superior or inferior vena cava, outside the pericardial reflection [80]. Common indications for PICC placement include parenteral nutrition and need for long-term IV medication (antibiotics for bacterial, fungal, or viral infections). PICC has significant risks and complications (such as sepsis) and must be avoided when peripheral venous access is adequate and possible [80]. Many neonatologists prefer to place a PICC after 24 h of parenteral antibiotics or when the blood culture is no longer positive for infection. Strict aseptic precautions must be followed when placing the catheter

A central venous catheter is usually inserted percutaneously in neonates. A cutdown or surgical technique is used only when percutaneous insertion has been unsuccessful. Adequate sedation and analgesia should be provided before beginning to insert the catheter. A slow infusion of 2–4 mcg/kg of fentanyl is preferred, although larger doses may be required for infants who have developed tolerance to opioids and in infants whose lungs are mechanically ventilated. Infants who do not require significant respiratory support may receive non-pharmacologic comfort measures such as sucrose-dipped pacifier in addition to fentanyl. For catheter insertion by surgical cutdown, local infiltration with lidocaine is recommended.

It is important to check the position of the catheter tip before commencing surgery. The use of radio-opaque con-

trast improves localization of the catheter tip. The most recent chest radiograph should be evaluated for catheter position. Catheters have been reported to migrate, and these have been associated with complications after insertion.

Most indwelling catheters are made of silicone or polyurethane to minimize the risk of perforation and fracture. In neonates, small gauges (1.1, 1.9, 2, and 3 Fr) are commonly used for percutaneous insertion. These catheters offer too much resistance to allow withdrawal of blood or to rapidly infuse fluid boluses, anesthetic induction drugs (such as propofol), or blood products during surgery. Sterile precautions should be observed when breaking into a PICC circuit during surgery.

Anesthesia Requirements

There are several important issues that the anesthesiologist should establish when planning to provide anesthesia in the NICU (Table 13.4). First, dedicated IV access should be available to administer drugs and fluids. A second, separate IV access should be available to administer drugs such as antibiotics or vasopressors. Second, the anesthesia regimen most frequently used for neonatal surgery is an opioid-based technique with neuromuscular blockade. Fentanyl is the most widely used opioid in neonates. Most surgeries require muscle relaxation, and rocuronium or vecuronium is the most commonly used neuromuscular blocking agent. All medications should be flushed through the line as medications are often administered at a site remote from the infant and may cause an unexpected delayed effect when the IV line is later flushed. All fluid boluses, flushes, and infusions should be carefully documented to prevent fluid overdoses. There have been some reports of the adjunct use of midazolam and propofol [81] in neonates during surgery in the NICU. The potential for profound circulatory depression after use of these drugs, especially in the septic or compromised neonate, cannot be overstated. Midazolam has no role in neonatal intubation and surgery as the pharmacology of this drug, especially in preterm neonates, is unfavorable and potentially harmful (see below, ref. 82). Most neonates are volume contracted in the NICU resulting in both direct and indirect vaso−/venodilatation when anesthetics are administered, resulting in reduced preload and afterload. The intubating dose of propofol used as the sole anesthetic, has been conflicting, although there is some evidence 2 mg/kg is generally effective. However, the consequences have included both profound and prolonged hypotension particularly in VLBW infants [83–85].

Table 13.4 Anesthesia requirements

IV access
Drugs
Anesthetic technique
Monitoring
Ventilation
Fluids

In our institution, the NICU team infuses 10 mcg/kg fentanyl over 20 minutes *before* the anesthesia team arrives in order to assess the risk of hypotension and, if necessary, to restore euvolemia and blood pressure using balanced salt solution. If fluid boluses are needed, then euvolemia will be established before additional fentanyl and paralysis are given at the time of skin incision, thereby minimizing the risk of post-induction or post-incision hypotension. Our goal is to maintain cardiorespiratory homeostasis at the time of and after skin incision. Abdominal surgery often requires fentanyl doses as little as 10–20 mcg/kg, whereas thoracic surgery may require fentanyl doses (over the duration of the surgery) of 30–50 mcg/kg [86, 87]. It should be appreciated that the elimination half-life of fentanyl in preterm neonates is variable, with markedly prolonged elimination in neonates with increased intra-abdominal pressure (IAP) [86, 88]. Paralysis should be administered to provide adequate surgical relaxation while monitoring ventilation and oxygenation carefully, as pre-paralysis settings may lead to hypercapnia once paralysis is provided or desaturation if tidal volumes are insufficient.

Many neonates are not paralyzed in the NICU, and as such there is often some degree of spontaneous respiration either with conventional ventilation or HFOV. In some cases, loss of this spontaneous respiration component will cause significant hypercapnia which could result in pulmonary hypertension, hypoxia, and hypotension. To avoid surprises, paralysis with appropriate sedation should be administered before surgery commences to allow sufficient time to assess any negative effects of these agents on the cardiorespiratory systems. Otherwise, this deterioration may be confused with ventilator insufficiency due to the effects of the surgical presence in the abdomen.

The monitoring equipment used in the NICU is often foreign to the anesthesiologist. Assistance is often needed from the bedside nurse or neonatologist to activate the audible pulse oximetry/ECG tones, which are frequently muted in the NICU. Blood pressure may be measured invasively via a radial or umbilical artery line, but in those in whom invasive pressure monitoring is not present, a noninvasive oscillometric blood pressure monitor should be used. The reliability of noninvasive measures of blood pressure monitoring in premature infants has been affirmed by some and questioned by others [89, 90]. Recent evidence supports applying the blood pressure cuff in either the upper or lower extremity in infants >1000 g but may provide more accurate readings from the lower extremities in infants <1000 g [91]. Mean and systolic blood pressures in premature and full-term neonates increase

with gestational age, birth weight, and postnatal age [92]. Of importance is the observation that the systolic and mean blood pressures measured noninvasively in premature and full-term neonates asleep is 10–20% less than the corresponding awake values [92]. This is consistent with the expected decrease in systolic blood pressure of 20–30% with induction of anesthesia. Because complex ICU ventilators or HFOV/HFJV are often used in the NICU, a neonatologist and respiratory therapist should be present throughout the procedure [43] to assist with ventilation, oxygenation, and ventilator-related issues. Changes in oxygenation and ventilation may occur as a result of increases in the abdominal pressure and/or decreases in lung compliance associated with surgery. Persistent changes in oxygenation and ventilation may require compensatory changes in PEEP, PIP, and mean airway pressure depending on the mode of ventilation as well as the inspired fraction of oxygen. If conventional ventilation cannot maintain adequate blood gases, it is possible that the strategy will have to be changed to perhaps HFOV [93]. Neonates whose lungs require HFOV are often monitored using transcutaneous CO_2 monitoring. This monitor tracks the $PaCO_2$ [94] although it requires recalibration periodically; the response lags compared with end-tidal capnography and its accuracy should be confirmed by comparing the results to an arterial blood gas before commencing surgery [56]. Capnography is not routinely available in most NICUs, but the anesthesiologist should ensure that capnography is available for those neonates and VLBW infants with reasonable lung function and whose lungs are ventilated with conventional ventilators [55, 94–96]. End-tidal CO_2 does not provide accurate estimates of $PaCO_2$ in neonates whose lungs are ventilated with HFOV (see discussion on high-frequency ventilation below).

Thermoregulation is a vital function in the neonate that may prove challenging during surgery in the NICU. Surgery is often performed in open radiant warmers with overhead radiant heaters in the NICU. However, these heaters may be less effective at maintaining thermoneutrality during surgery as the surgeons cover the neonate blocking the infants from the heat source. In the OR, the ambient temperature is often increased to 26 °C [97–99] to prevent radiation and, to a lesser extent, convective heat losses (see Chap. 8). This is not usually possible in the NICU setting unless a designated procedure room is used. A forced-air heating blanket, which is a very effective method to prevent intraoperative hypothermia [100] better than most other strategies during surgery, is usually unavailable in the NICU. However, if it is available, it should be placed under the infant before surgery commences. A fluid warmer should be used to warm all fluids, especially if blood products are required. Often, a fluid warmer must be supplied from the OR. Hypothermia during neonatal surgery has been associated with reduced OR ambient temperature as well as with major surgical procedures [57], e.g., open abdominal procedure. Similar data from the NICU have not been forthcoming.

One major controversy regarding surgery in the NICU when this subject was initially considered was the potential risk for increased infections and sepsis. However, several small studies failed to demonstrate any increased risk associated with operating in the NICU. One study that involved repair of CDH in the NICU [57] reported an increased but not statistically significant change in the infection rate. However, they did demonstrate a significant increase in the inflammatory marker C-reactive protein (CRP) in the NICU operative group, suggesting that inflammation was present. Because critically ill neonates are more prone to infections as well as a greater morbidity and mortality from infection than healthy neonates, it is imperative to adhere to OR infection control policies including the use of appropriately timed (pre-incision) surgical site antibiotics irrespective of the location of the surgery [53].

Published reports of neonates undergoing a variety of different operative procedures in the NICU have included small samples and were retrospective in nature, and none were randomized trials evaluating outcomes. A review of the publications to date suggests that the neonates in the NICU operative group had a greater mortality than those operated in the OR [41, 48, 81, 101], although selection bias limits the external validity of these data: these neonates were sicker and required more ventilatory and inotropic support. The extent to which these differences of pre-procedural morbidity were responsible for the increased mortality is difficult to determine. A retrospective study [41] utilizing the score for neonatal acute physiology (SNAP) demonstrated that neonates undergoing surgery in the NICU had a greater preoperative SNAP score than those undergoing surgery in the OR but that SNAP increased by 20% in both groups during the initial 24 h post-procedure.

Despite the lack of evidence concerning improved outcomes after surgery in the NICU, it is difficult to determine whether the challenges associated with undertaking surgery in a foreign environment offset those associated with transferring the neonate to the OR [41]. As surgery is performed more frequently in the NICU on more stable neonates, the mortality rate is decreasing significantly [41]. In many centers today, surgery in the NICU is regarded as routine and safe.

Sedation and Analgesia for Common Procedures in the NICU

Critically ill neonates undergo frequent painful procedures such as blood draws, heel sticks, and intravenous catheter placement in the NICU daily [102]. Other procedures that may cause discomfort in some neonates include tracheal intubation, mechanical ventilation, and tracheal suctioning

[103]. Neonates who require mechanical ventilation are often sedated with a combination of fentanyl and midazolam. The American Academy of Pediatrics (AAP) published guidelines for premedicating neonates who require nonemergent tracheal intubation [82]. They recommended atropine, fentanyl as a slow infusion, and vecuronium/rocuronium. These guidelines recommend avoiding midazolam in premature neonates because of its prolonged half-life, hypotension, reduced cerebral blood flow, and the presence of benzyl alcohol as a preservative. Despite these recommendations, a survey of NICU practices from the AAP 5 years later, in 2015, reported only one-third of neonatologists frequently use premedication and less than 50% of the institutions have written protocols for premedicating neonates before intubation [104]. In a survey of NICU practices in 70 countries during the period 2018–2019, the attitudes and practices to nonemergency intubations in neonates were wide-ranging, with up to 12% reporting they used no premedication whatsoever [105]. The authors called for an international consensus to formulate optimal practices for intubation in neonates.

High-Frequency Ventilation

Critically ill neonates, especially premature infants, may develop hypoxemic respiratory failure as a result of small lung volumes, poor compliance, increased intra- and extrapulmonary shunts, and ventilation perfusion mismatch. High-frequency ventilation is a commonly used lung-protection strategy that benefits oxygenation and ventilation [93]. Two types of high-frequency ventilators are used in neonates in the United States:

1. High-frequency oscillatory ventilation (HFOV, Sensor Medics 3100A, CareFusion Corporation, San Diego CA) utilizes a piston pump to generate oscillations [106]. This is the only mode of ventilation in which inspiration and expiration are active. A constant distending pressure is applied to the lungs (mean airway pressure), over which small tidal volumes (amplitude) are superimposed at a rapid respiratory frequency (6–15 Hz). Typically a frequency range between 10 and 15 Hz is used in neonates. Greater frequencies are commonly used in premature infants. The frequency of oscillation influences the CO_2 removal in a direction opposite to that of conventional ventilation. Greater frequencies decrease tidal volume and increase $PaCO_2$. Decreasing the frequency and increasing the amplitude independently increase tidal volume and decrease $PaCO_2$. The following factors should be considered if a critically ill infant who depends on HFOV requires surgery:
   (a) Performing surgery while the lungs are ventilated using a HFOV may be technically difficult for the surgeon.
   (b) Mean airway pressure recruits alveoli and is closely related to oxygenation. When an infant is switched from conventional ventilation to HFOV, it is recommended that the starting mean airway pressure be 2 cmH_2O above the mean airway pressure on conventional ventilation.
   (c) If a neonate is weaned from HFOV to conventional ventilation for surgery, adequate PEEP must be provided to maintain alveolar recruitment and oxygenation.
   (d) Increased mean airway pressure can impede venous return and decrease blood pressure. If hypotension is encountered during HFOV, fluid boluses may be required. If hypotension persists, the mean airway pressure should be decreased providing the respiratory status of the neonate remains stable.
   (e) Wide fluctuations in $PaCO_2$ (especially hypocarbia) can occur during HFOV. Frequent blood gases and/or transcutaneous pCO_2 monitoring provide useful indices of ventilation with HFOV; end-tidal pCO_2 monitor is unreliable. The skin at the site of transcutaneous monitor application must be frequently checked to avoid burns. The site may have to be changed frequently particularly in premature infants.
2. HFJV (Life Pulse, Bunnell Incorporated, Salt Lake City, UT) is the second form of high-frequency ventilation in the Unites States. HFJV is particularly effective for early intervention and treatment of pulmonary interstitial emphysema [107]. The jet ventilator provides small, high-velocity breaths and fast rates with passive exhalation. A conventional ventilator operates in tandem with the jet ventilator to maintain optimal PEEP. The conventional ventilator is attached to the regular connector of the TT, and the HFJV is connected through a special adaptor to the side port of the tube. Mean airway pressure is adjusted primarily by changing the PEEP on the conventional ventilator. Just as in the case of conventional ventilation, faster respiratory rates and greater PIP with the HFJV reduces the $PaCO_2$. See Chap. 9 for further information.

Transport

The majority of births in the United States occur in hospitals without tertiary-level neonatal intensive care units (NICUs). Neonates who are born extremely premature outside a tertiary hospital may require transport to a tertiary hospital (interhospital transport) soon after birth because of respiratory distress, congenital anomalies, and/or surgical problems. A transport incubator should be used for all interhospital transports. Once inside the tertiary hospital, these neonates may require transport within the facility for diagnostic or special procedures such as radiography, cardiac catheterization, or

surgery [108] (intrahospital transport). Many of these neonates are critically ill, require mechanical ventilation, and are at increased risk for cardiorespiratory instability. Increased stimulation during transport can destabilize a critically ill infant. Accordingly, appropriate sedation and analgesia during transport will prevent cardiorespiratory instability.

For short transports within the hospital, critically ill infants are transported on radiant warmer beds. In these instances, the infant's head should be covered with a hat, and the body wrapped in a plastic/vinyl insulated bag to prevent heat loss. In neonates with abdominal wall defects (gastroschisis or omphalocele) or large neural tube defects (meningomyelocele and encephalocele), sterile vinyl bags should be applied to prevent infection, hypothermia, and hypovolemia. Intrahospital transports are best managed by manually ventilating the lungs. Hand ventilation enables the operator to continuously evaluate the compliance of the lungs including early detection of accidental extubation, a tube disconnect or TT kinking, or occlusion to be detected earlier although this depends on the fresh gas flow and operator experience [45]. However, if the lungs are ventilated manually, it is imperative that the operator remains focused on the ventilation (rather than steering the incubator) to ensure the respiratory rate and peak inspiratory pressure are appropriate.

It is recommended that the neonatal transport team carry medications for analgesia, sedation, and paralysis [108] including analgesics and sedatives (fentanyl, morphine, midazolam), neuromuscular blocking drugs (pancuronium and vecuronium), and reversal agents (flumazenil to reverse benzodiazepines, naloxone to reverse opioid-induced respiratory depression, neostigmine to antagonize neuromuscular blocking agents). In addition, they must have equipment to manage a sudden airway emergency including an appropriately sized laryngoscope, TTs, stylet, and ventilation circuit (Ambu bag or T-piece).

Specific Conditions Requiring Surgery in the NICU (For Further Details, See Chap. 9 "Thoracoabdominal Surgery")

Closure of PDA

Failure of the PDA to close spontaneously or in response to medical management with indomethacin or ibuprofen is common in ELBW premature infants. Medical management appears to fail in up to two-thirds of ELBW infants [109]. When medical treatment was compared with surgical closure of the PDA as first-line therapy in premature infants, the incidence of mortality and post-closure complications were similar [110]. In some, medical treatment may be contraindicated because of IVH or renal failure. A PDA results in significant left-to-right shunting of blood causing pulmonary overcirculation, respiratory failure, prolonged ventilator dependence, congestive cardiac failure and chronic lung disease, and necrotizing enterocolitis (NEC). In these patients, surgical ligation of the PDA may be performed [109]. More recently, percutaneous closure of the PDA has been performed successfully in young neonates and may point to another approach to open surgical ligation [111].

Surgical ligation of a PDA in neonates has a low morbidity and mortality. The CXR may indicate fluid overload or evidence or a respiratory distress syndrome (RDS). The echocardiogram establishes the size of the ductus and the degree and direction of blood flow. Although surgical closure of the PDA is routinely performed in the OR, it has also been performed in the NICU [112]. PDA closure appears to be the most common surgical procedure performed in the NICU. Multiple studies from worldwide report that over 700 neonates have received PDA closure in the NICU without major complications [113]. The outcome from surgical ligation appears to be related to the underlying degree of pulmonary and cardiovascular disease. In a nonrandomized study of PDA ligation in the OR and NICU, it demonstrated that postoperative mortality (17%) was due to respiratory failure and sepsis, with risk factors being surgery in the NICU and low birth weight [114]. The overall outcome of PDA ligation was early extubation (<10 days) in 30% of neonates, late extubation (no chronic lung disease, CLD) in 22%, and late extubation with CLD in 31%. There was no difference among the groups in terms of early incidence of extubation suggesting that the outcome after PDA closure in neonates without severe cardiorespiratory disease is similar, whether it is completed in the OR or NICU. In another study of 41 PDA ligations in neonates <1500 g with a mean gestational age of 27 weeks in the NICU, none of the complications were attributable to anesthesia. The five deaths were all related to prematurity and congestive heart failure [112].

A retrospective study of 189 premature infants compared perioperative complications after PDA ligation in the NICU or OR. Mortality and sepsis after ligation in the NICU was similar to that in the OR, although hemodynamic instability was significantly more frequent during transport from the OR to the NICU [47].

In some institutions, ligation of a PDA in the NICU is considered standard. Some regional centers have a team comprising of a pediatric cardiac surgeon, pediatric anesthesiologist, and pediatric OR nurses traveling to pediatric hospitals to perform PDA ligation in the referring hospital's NICU to avoid the interhospital transfer of the neonate [115]. There was no difference in either the preoperative complication rate or mortality between these neonates and those operated on at the surgical institution. Most importantly, by not transferring the neonates, the same neonatal team that is most familiar with the infant's medical and social history could provide the infant's care, and the family is minimally inconvenienced.

With the approval of a new device in 2019, transcatheter occlusion of PDA is being increasingly preferred over surgical ligation (see cardiac catheterization section below).

NEC

NEC is the most common gastrointestinal surgical emergency in premature neonates, [116] affecting approximately 6–7% of VLBW infants. Full-term infants rarely present with NEC. The pathogenesis of NEC remains unknown, but it is quite likely a multifactorial disease. Risk factors include prematurity, enteral feeding (especially formula), infection, and ischemia (Fig. 13.5). Classic radiographic findings include gas in the intestinal wall (pneumatosis), air in the branches of the portal vein and biliary tract, and free air within the abdomen (Fig. 13.6). Indications for surgical exploration include intestinal perforation with pneumoperitoneum or continued clinical deterioration despite maximal medical management. Surgical management with a peritoneal drainage is often favored in an unstable, critically ill premature infant with the caveat that a subsequent laparotomy may be required if the condition deteriorates.

Neonates who require surgery for NEC are usually critically ill and require intensive resuscitation before surgery. Preoperative management before exploratory laparotomy should address the following issues:

(a) Blood pressure: Hypotension is common in NEC and is secondary to third spacing of fluids in the abdomen, capillary leak, high peak inspiratory pressures, sepsis with poor vascular tone, and low cardiac output. Fluid boluses (both crystalloids and colloids) may be required repeatedly until the vital signs stabilize. Many infants require inotropic support with dopamine and/or epinephrine.
(b) Respiratory failure: Pulmonary edema and acute respiratory distress syndrome (ARDS) are commonly associated with fulminant NEC. Infants require high peak inspiratory pressures during conventional ventilation. Some infants may be so ill that their lungs require HFO (see discussion above).
(c) Electrolyte and acid–base disturbances: Fulminant NEC results in respiratory and metabolic acidosis.

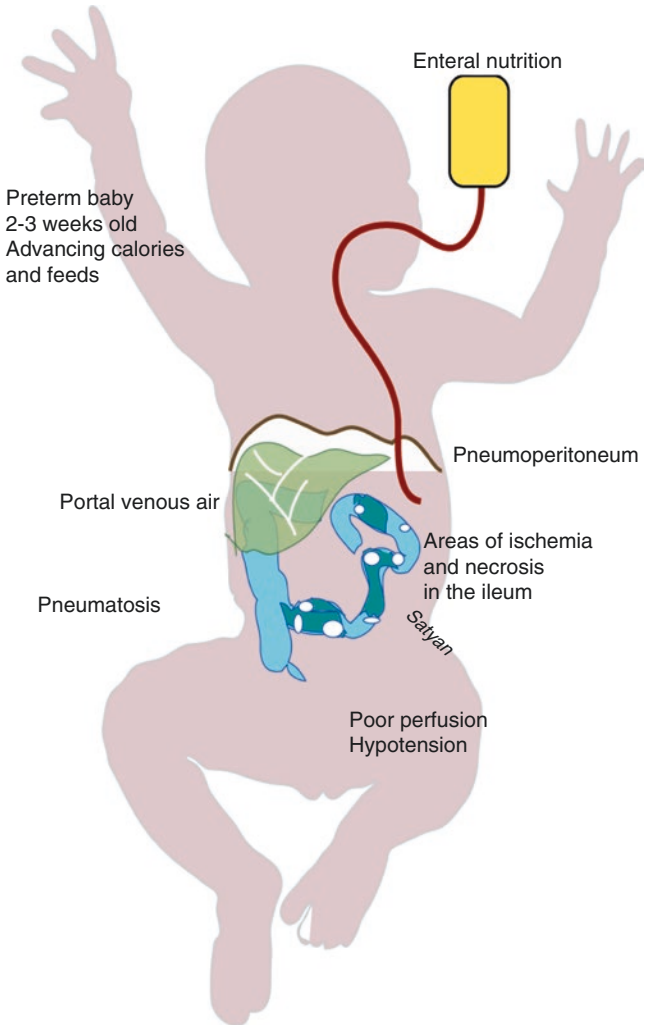

Fig. 13.5 Pathophysiology of NEC requiring surgery. A typical patient is a premature infant approximately 2–3 weeks of age, taking advancing feeds. The terminal ileum is commonly involved. Areas of ischemic necrosis and pneumatosis (intramural collection of air) are observed in the ileum. Portal venous air can be visible on abdominal X-ray. Pneumoperitoneum is the most common indication for surgery in these infants

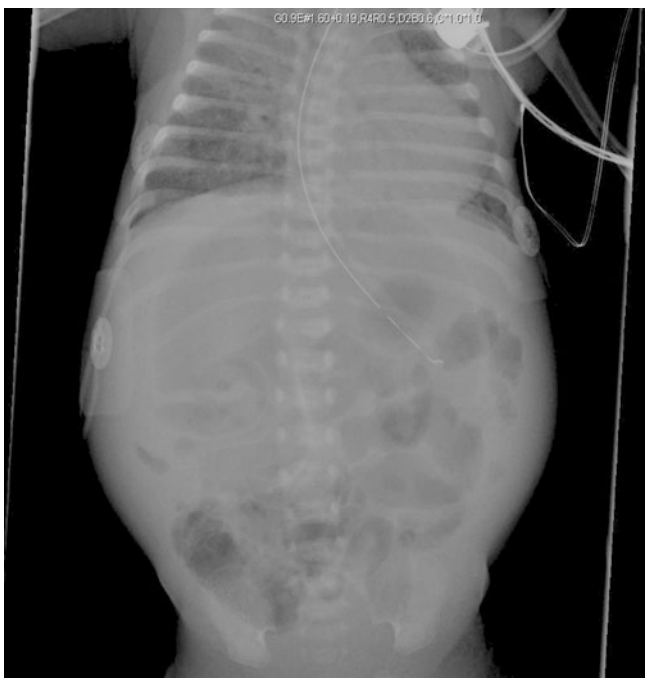

Fig. 13.6 X-ray showing pneumoperitoneum (anterior to the liver), pneumatosis in a patient with NEC prior to surgery

Table 13.5 Average perioperative resuscitation requirements for NEC patients in the NICU

Inotropes, e.g., dopamine	Increased dose by 4 mcg/kg/min
Bicarbonate	2.5 mmol/kg
Blood	32 mL/kg
Platelets	12 mL/kg
FFP	15 mL/kg
5% albumin	35 mL/kg

Hyponatremia is common secondary to third spacing, and hyperkalemia due to acidosis occurs in some infants and may need to be corrected either before or during surgery. Hypocalcemia secondary to multiple blood product infusion may exacerbate hypotension and should be avoided.

(d) Hematologic disturbances: A review of 25 neonates who required surgery for NEC in the NICU required many blood products perioperatively (Table 13.5) [35]. This report illustrates the need to have blood products immediately available for the anesthesiologists to administer during the procedure. Thrombocytopenia occurs commonly in NEC. NEC associated with ischemic or necrotic bowel may also present with disseminated intravascular coagulation (DIC). PT, PTT, fibrinogen, and fibrin split products should be frequently monitored along with complete blood counts in neonates with NEC. Transfusions with packed red blood cells (PRBCs), fresh frozen plasma (FFP), and platelets are often required.

Many neonates with NEC may have received systemic glucocorticoids for hypotension or management of BPD. Such patients may need a stress dose of glucocorticoids before surgery.

(e) Vascular access: At least two peripheral intravenous catheters are recommended during surgery for NEC. A central venous catheter is useful to infuse inotropic agents (since most neonates will require support) and an arterial catheter to monitor blood pressure continuously and sample arterial blood.

General tracheal intravenous anesthesia with neuromuscular blockade is preferred for NEC surgery [39]. Lung ventilation is commonly managed with a standard neonatal ventilator, rendering an intravenous anesthetic approach preferable over inhalational anesthetics. A high-dose opioid technique with intravenous fentanyl (20–50 mcg/kg), midazolam (0.1 mg/kg), and a muscle relaxant is often used. Hypotension is common after induction of anesthesia but can be prevented in most infants by preinfusing 10–20 mL/kg of balanced salt solution such as normal saline or lactated Ringer's solution. Persistent hypotension despite fluid resuscitation may necessitate the use of inotropes such as dopamine and stress dose glucocorticoids. Third space losses are common during surgery in NEC, and many infants require 50–100 mL/kg of fluid during surgery. Depending on the type of fluids administered preoperatively and laboratory indices, this may include balanced salt solution, colloid, or blood products (PRBCs, FFP, and platelets). Infants with NEC continue to require large fluid volumes in the postoperative period because of ongoing third space losses, and this must be born in mind during the postsurgical period.

Table 13.6 Location, extent of disease, and mortality for NEC [117]

Location	% Bowel involved	% Mortality
Ileum	15	15
Large bowel	20	35
Jejunum–ileum	65	80
Large bowel–ileum	35	40
Large bowel–jejunum–ileum	85	95

The mortality for NEC surgery in the NICU has been reported to be as great as 50%. Mortality is affected by several variables including the location and extent of the disease (Table 13.6) [117]. Neonates with extensive NEC are those in whom surgery is undertaken preferentially in the NICU, and it is in those neonates that the mortality is significantly greater. In neonates with NEC who are the most unstable, placement of a peritoneal drain in the right lower quadrant is usually sufficient [42].

SIP

A subset of premature neonates who present with intestinal perforation without signs of NEC, such as pneumatosis intestinalis, are classified as focal or SIP. This condition presents early (7–10 days of age) in ELBW infants [118, 119]. Prior exposure to early postnatal steroids and indomethacin may be risk factors for SIP [120, 121]. Although these neonates are not as sick as those with advanced NEC, they tend to be much younger, their lungs are often mechanically ventilated, and they have umbilical lines secondary to their RDS at birth (Fig. 13.7). Surgery for SIP often involves resection of the perforated site and reanastomosis or ileostomy. This procedure is often done at the bedside in the NICU because of the young gestational age.

Gastroschisis

Gastroschisis is a nongenetic, anterior abdominal defect that has an unclear etiology, with one theory being it results from an occlusion of the omphalomesenteric artery (see Chap. 9). Gastroschisis, located in the periumbilical region usually on the left side, includes small and large intestines and other abdominal organs that are free-floating in amniotic fluid during fetal life. The chronic exposure of these organs to amni-

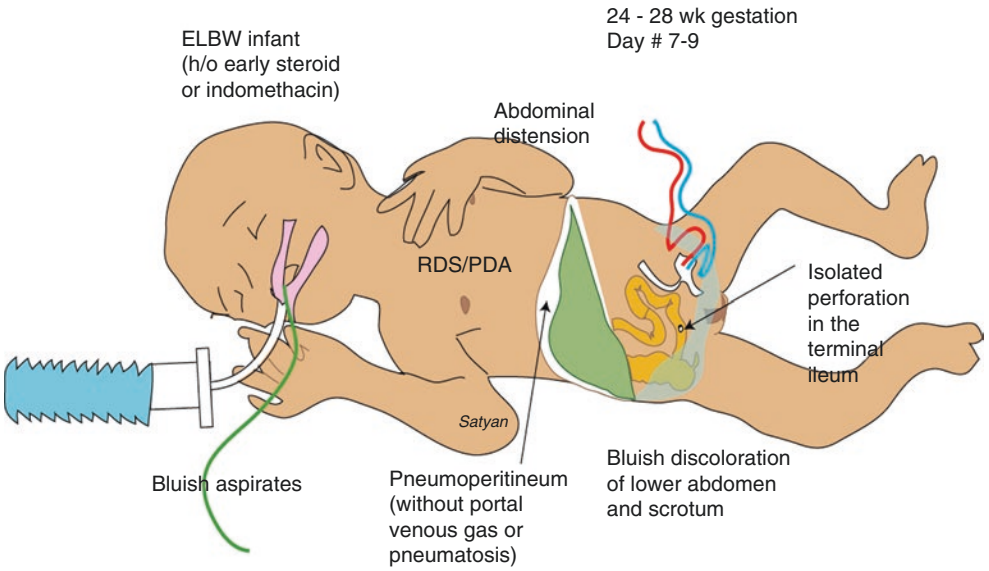

Fig. 13.7 A typical patient with SIP. These patients are of extremely low gestational age (median—26 weeks), presenting often with asymptomatic pneumoperitoneum by days 7–9. Some patients may present with bluish discoloration of the abdomen. There is no evidence of pneumatosis or portal venous air. Many of these infants are still on respiratory support for RDS and/or PDA and may have umbilical lines from birth. Pathology shows a perforation in the ileum without any evidence of coagulative necrosis, a finding commonly associated with NEC and ischemia

otic fluid causes inflammation and edema on the serosal surfaces that leads to the formation of a peel on the bowel surface. Preoperative management consists of reducing fluid loss from the eviscerated organs and bowel by administering adequate intravenous fluids in the form of boluses of normal saline or lactated Ringer's solution to replace third space and evaporative losses and covering the bowel with sterile, saline-soaked dressings and placed in a sterile plastic wrap. Gastric decompression is important to prevent distension of the stomach and intestines and reduce IAP. Reduction of gastroschisis and primary abdominal wall closure is commonly performed in the OR. This procedure may be associated with increased IAP. Central venous pressure > 4 mmHg, intravesical or gastric pressure > 20 mmHg, and splanchnic perfusion pressure (mean arterial pressure, IAP, <44 mmHg) during the primary repair suggest decreased splanchnic and renal blood flows. To preclude bowel and renal ischemia, it may be critical to abort the primary wall closure and opt for a staged repair (see below) to permit the anterior abdominal wall to stretch to accommodate the increased abdominal contents upon skin closure [122].

In some patients when the volume of eviscerated bowel is large relative to the volume of the abdominal cavity or when the IAP increases during attempted primary repair, staged reduction may be performed in the NICU. The staged repair consists of covering the eviscerated contents with a prosthetic silo pouch. The pouch is serially reduced in size in the NICU, allowing the abdominal cavity to gradually expand to accommodate the increased volume within, without severely compromising ventilation or organ perfusion. Careful inspection of the bowel for obstructing bands, perforation, and atresia should be undertaken before applying the silo. More recent introduction of a prefabricated silo with a circular spring that can be placed into the fascial opening, without the need for sutures or general anesthesia, has made it possible to insert the silo in the delivery room or at the bedside in the NICU [122]. These procedures are performed with intravenous opioid (2–4 mcg/kg of fentanyl) and midazolam (0.1 mg/kg). A PICC line must be placed in all infants with gastroschisis for total parenteral nutrition because intestinal hypomotility and delayed initiation and advancement of oral feeds are common.

Retinopathy of Prematurity (See Chap. 2)

The surgical management for ROP may involve both laser and cryosurgery. There are numerous reports of these procedures being performed in the NICU [123] and the OR. These neonates are not usually critically ill, thus reducing the risk of transporting these neonates to the OR. Nonetheless, performing these procedures in the OR is believed to delay their care. This prompted the practice of evaluating and managing these infants in the NICU. In the NICU, local anesthesia and IV sedation have been used, although emergent airway management has been common. Presently, neonatologists use a local anesthetic/sedation technique and sedation/analgesia/paralysis technique with tracheal intubation or maintain their present level of respiratory support to facilitate these procedures in the NICU [124–127].

CDH

The management of CDH now often includes NICU management with HFOV, surfactant, inhaled nitric oxide, and possibly ECMO (in up to one-third of neonates with CDH), followed by delayed surgical repair [128]. The decision to repair CDH in the NICU is often determined by the ventilatory management required to support the infant. Despite an increasing proportion of neonates undergoing corrective repair of CDH, present survival rates in a background of HFOV, iNO, and ECMO have not changed from 65% to 80% [129]. Supporting the infant for several days allows the severity of the pulmonary hypertension to improve and vessel reactivity to wane. Although initially unstable (Fig. 13.8), these infants can stabilize and progressively improve resulting in better gas exchange and increased lung compliance during postnatal adaption and correct management strategies. Those infants with significant pulmonary hypoplasia (15%) or an abnormal persistence of the pulmonary hypertension may fail to stabilize postnatally and may require ECMO. Neonates with CDH who also present with congenital heart defects (incidence ~10%) present a heterogeneous group of heart defects that pose a daunting challenge. ECMO has been used to support these infants with survival rates for single ventricle physiology that were similar to those with CDH without a heart defect [130]. Retrospective data suggest that blood gases in the first 4 h after birth may predict outcomes in terms of ECMO requirement and mortality [131]. Those who recommend surgical repair in the NICU do so to avoid the logistical difficulties and patient safety issues associated with transferring the neonate, who depends on HFOV, iNO, and/or ECMO, to the OR. If the lungs require HFOV to maintain the pCO_2 in an acceptable range and the child is scheduled for surgery in the OR, converting the ventilation mode to conventional ventilation may be considered provided the respiratory settings do not exceed those shown in Table 13.7 [81]. If the respiratory indices remain within acceptable limits after conversion to conventional ventilation, the infant may be transferred to the OR 24 h later.

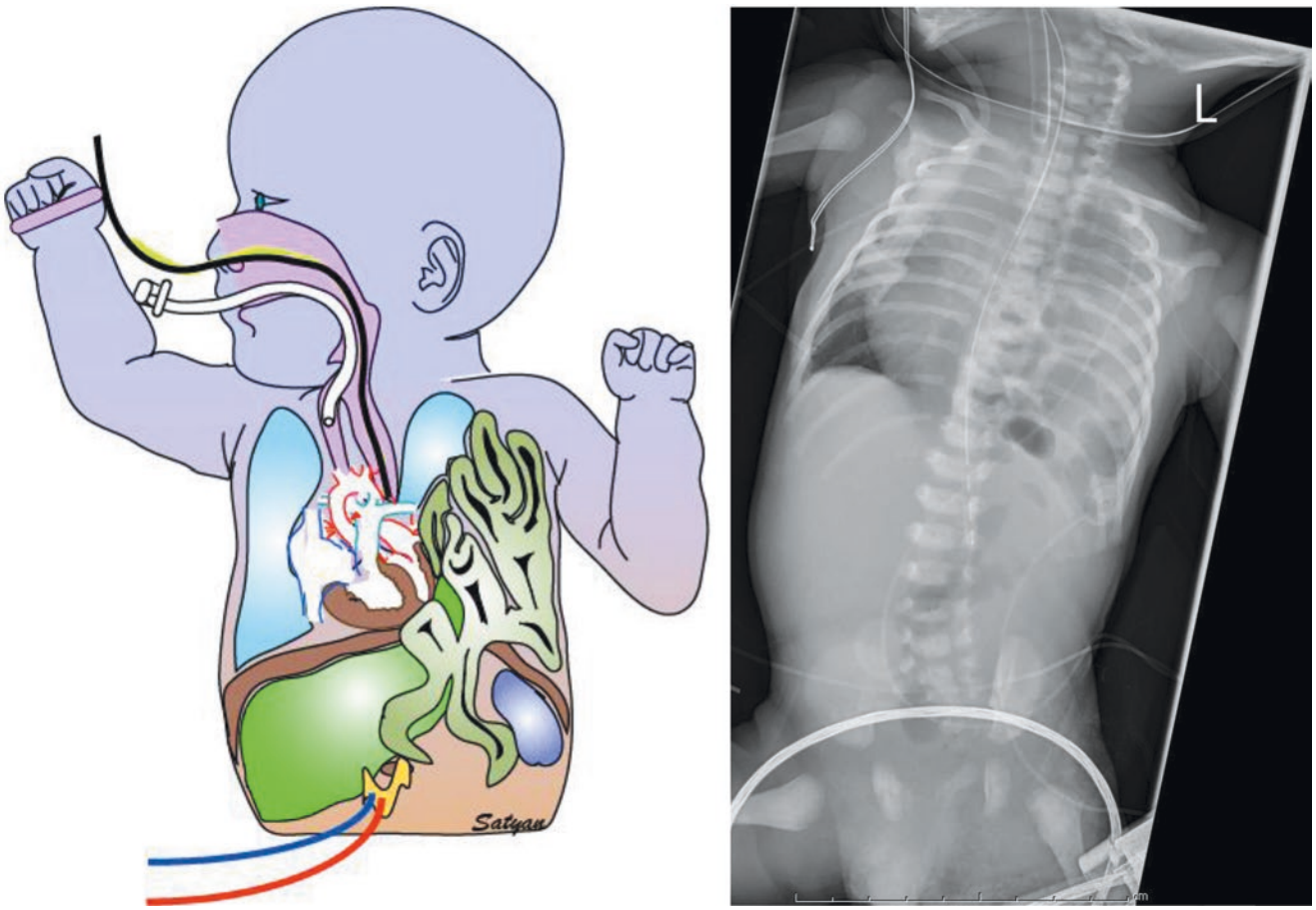

Fig. 13.8 CDH. The schematic on the left illustrates the presence of bowel in the left chest displacing the heart to the right and compressing the right lung as shown in the radiograph on the right. The radiograph reveals an infant whose airway was intubated and whose bowel was present in the left chest. The diaphragmatic defect was not diagnosed antenatally. Feeding commenced after birth in the newborn nursery before the diaphragmatic hernia was diagnosed [147]

Table 13.7 Recommendations for the transition from HFOV to conventional ventilation for CDH repair

After at least 72 h since birth, with minimal inotropic support, HFOV settings should be:
FiO_2 <0.4
MAP <13 cm H_2O
Amplitude <30 cm H_2O
Oxygenation index <10
No ultrasound evidence for pulmonary hypertension
No difference in pre- and postductal SaO_2
Pulmonary/systemic pressure ratio <0.75
Stable with above criteria for 24 h

A comparison of neonates after CDH surgical repair using fentanyl, pancuronium, and occasional midazolam and propofol anesthesia in the NICU and the OR demonstrated a greater mortality in the former, 33%, compared with the latter, 7% [81]. The NICU infants required more inhaled nitric oxide, greater mean arterial pressure, greater need for inotropic support, and a greater oxygenation index (mean airway pressure × FiO_2 × 100 ÷ postductal PaO_2, usually the umbilical arterial PaO_2).

Other Reported NICU Surgical Procedures

Several additional procedures may be undertaken in the NICU [113]. For posthemorrhagic hydrocephalus in VLBW infants, a VP shunt, external ventricular shunt, or more commonly a ventricular reservoir for intermittent tapping may be performed [132]. Tracheostomies have been performed in the NICU as reported in both pediatric and adult intensive care literature. Also, urogenital procedures including urinary diversion procedures such as a nephrostomy or ureterostomy may be suitable to perform in the NICU.

Sedation for Imaging Procedures (MRI/CT)

Sedation is often required for neonatal patients requiring radiological procedures such as MRI or CT scan [133]. Standard anesthesia monitors that are compatible with both MRI and CT equipment are available and should be used. However, temperature monitoring during MRI scans may not be available. All monitoring wires should be straight (not coiled) and probes placed as far from the magnetic coil as possible to diminish the possibility of thermal injury. Medications and/or procedures used for sedation depend on the age and cardiorespiratory status of the infant. Many infants less than 3 months of age without any cardiorespiratory compromise can be fed and wrapped snugly for an MRI and CT without sedation [134].

A topic for debate at present is whether the risk of a CT scan with its ionizing radiation exposure is less than the risk of an MRI scan with anesthesia. In general, a cumulative radiation exposure of 100 mSv is the threshold considered to increase the risk for malignancy; this dose is consistent with multiple CT scans. However, there is also a concern that perhaps any exposure above zero exposure increases the risk for malignancy. Factors such as a variability in sensitivity to ionizing radiation damage, gender, and the ability to use low-dose CT scans can alter the risk–benefit ratio. The MRI itself is generally considered safe with the appropriate use of gadolinium contrast in patients with renal dysfunction. However, there are the short-term risks from possible peri-anesthesia complications, as well as the potential long-term developmental risk. Some authors now support the use of low-dose CT scans rather than an MRI/GA combination for these reasons [135]. Given the growing concern over the possible neurotoxic effects of anesthetic drugs on the developing brain, more centers may consider the feed and swaddle technique as a first-line method for neonates to obtain brain MRIs, with sedation and GA reserved for failed feed and swaddle attempts and special circumstances.

Older infants may be given chloral hydrate, ketamine, midazolam, or several other sedatives for sedation with a similar rate of adverse events [136], although general anesthesia is more frequently required with appropriate airway management as an alternative to the complications associated with chloral hydrate sedation in young infants [137]. Full-term neonates may be sedated for CT scan after standard monitors are applied by simply inducing anesthesia with 8% sevoflurane, applying nasal prongs with 2 l/min oxygen, placing a roll under their shoulders, and allowing the scan to proceed while the neonate breathes spontaneously. Present CT scan imaging is so rapid that neonates often do not recover from the inhalational induction before the scan is completed. These same neonates may also require MRI, which usually lasts 1–2 h depending on the type of scan and the strength of the magnet. The approach to anesthesia in the neonate for an MRI scan begins with an inhalational induction with sevoflurane and nitrous oxide, followed by IV cannulation and discontinuation of the nitrous oxide. Most neonates with normal craniofacial anatomy and airways can be sedated for the scan using a continuous propofol infusion. The neonate is positioned supine with a small roll under the shoulders and the neck extended. Nasal cannulae are applied while the child breathes spontaneously and anesthesia maintained with a propofol infusion. Neonates and those who are cognitively impaired may require greater infusion rates of propofol than toddlers (who usually require 250–300 mcg/kg/min) to stop moving during scan. Propofol infusion rates in neonates are greater than in older children, reaching 400 mcg/kg/min at the beginning to transition from the sevoflurane induction and prevent movement during the initial scan. Thereafter, the infusion rate of propofol may be tapered to 250–300 mcg/kg/min. Respiration is monitored

using the baffled nasal cannula with a CO_2 sample line and pulse oximetry. Dexmedetomidine has been used for sedation for MRI scans in infants and children with non-instrumented airways using very large doses of 3 mcg/kg loading followed by 2 mcg/kg/h infusion [138], whereas we have shown that a small dose of IV midazolam (0.1 mg/kg) given at the beginning of the sedation allows for much smaller infusion rates of dexmedetomidine, 1 mcg/kg loading dose, followed by 0.5 mcg/kg/h [139]. There are no data regarding dosing of dexmedetomidine for sedation in neonates, although pharmacokinetic data suggests that the clearance of dexmedetomidine in neonates is one-third than in adults, which might mean that the infusion rate could be reduced [140]. In those with craniofacial and airway anomalies and in ex-premature infants (<60 weeks' postconceptional age), tracheal intubation (or an LMA) may be indicated to complete the scan [141].

Cardiac MRI

There is a growing use of cardiac MRI scans to diagnose cardiac disease in infants, including those in the NICU [142]. Cardiac MRIs are capable of imaging all of the thoracic organs, the respiratory anatomy, and cardiac function and anatomy in a single technique, without radiation exposure. Other benefits include avoiding the use of IV contrast and potential catheter-related complications [143]. In the critically ill neonate, monitoring both the arterial and venous pressures is important to titrate the dose of anesthesia and volume of fluids. Although cardiac MRI scans often require prolonged anesthesia, their duration is similar to that of diagnostic catheter procedures. Additional challenges during MRI in neonates include the limited access to the neonate while within the scanner, the need for an MRI-compatible anesthetic workstation, borderline reliable MRI-compatible neonatal monitors, and temperature control. The low ambient temperature required to cool the magnet combined with the neonate's inability to maintain normothermia and the lack of MRI-compatible effective warming devices increase the risk for hypothermia while the neonate is within the scanner. Consequently, neonates must be cocooned in warm blankets. Neonates under general anesthesia are four times more likely to become hypothermic as compared with fed and wrapped patients. Propofol appears to increase this risk when compared with sevoflurane [144].

Equipment challenges present a daunting financial obstacle if anesthetic services were included in the design of MRI units, although the capital cost of MRI-compatible anesthetic equipment is a very small fraction of the total cost of the MRI unit. MRI-compatible anesthesia workstations are available for use within the MRI scanner room. If an MRI-compatible workstation is not available, then the workstation must remain beyond the perimeter of the scanner, and long breathing circuit tubing must be fed through the copper hole in the wall to ventilate the neonate during a general anesthetic. Reliable monitoring is essential for all patients who require anesthesia for MRI. This is a particular challenge for infants as the monitors are often not optimized for very small patients. One of the more problematic monitors is the pulse oximeter, which often dislodges from the digit on which it was applied in neonates. In addition, there is often a limited choice of sizes of blood pressure cuff. Additional risks from the MRI environment include ferromagnetic projectiles that may kill the child within the scanner.

Cardiac Catheterization Laboratory

One of the most common areas outside of the NICU and OR where neonates require sedation and anesthesia is the cardiac catheterization laboratory. Transthoracic echocardiography in infants has a very good image window so that most cardiac diagnoses can be undertaken using noninvasive echocardiography. However, infants with complex cardiac abnormalities may require a diagnostic cardiac catheterization procedure to accurately determine the nature of the anatomy, function, and physiology as well as for cardiac interventions, often to increase pulmonary and aortic blood flows. This is more likely to be a concern in those infants who are critically ill in the NICU and may require the services of the pediatric anesthesiologist. In addition, MRI of the heart and lengthy electrophysiologic procedures such as radiofrequency ablation of aberrant conduction pathways, pacemaker insertion, and automatic implantable cardioverter defibrillator placements in infants have required the services of a skilled anesthesiologist knowledgeable in cardiac anesthesia for infants [145].

Often in non-OR anesthesia locations there are concerns that the anesthesia machine is often older and may be of an unfamiliar brand or model. The monitoring may not be as extensive or as up to date as in the OR. Providing anesthesia in a remote location also is complicated by the anesthesiologist being less familiar with the location, with limited assistance as well as possible inadequate communication with the off-site staff. These factors may be partly why closed claim analysis has demonstrated that these remote locations are more likely to suffer from serious complications [146]. A plan for communication within the off-site itself for emergencies as well as with the main OR is important to facilitate the best care possible.

Several common cardiac diagnoses that may require intervention are presented (Table 13.8). With the approval of the new Piccolo device (Abbott laboratories) for PDA occlusion in ELBW infants >700 g, in many institutions, surgical ligation is being replaced by transcatheter closure (Fig. 13.9). This procedure for the most part is performed in the cardiac

Table 13.8 Diagnosis requiring cardiac intervention

PDA closure
Balloon atrial septostomy—infants <8 weeks age for:
TGA—before switch procedure if hemodynamically unstable TAPVR with restrictive ASD Tricuspid atresia with restrictive ASD PV atresia with intraventricular septum
Hypoplastic left heart partially reduces gradient across atrial septum
Blade atrial septostomy > older than 8 weeks age: Same as per balloon septostomy
Balloon dilation of cardiac valves for: Pulmonary valve stenosis Aortic valve stenosis
Coarctation (NB., surgery is still the preferred treatment in neonate and infants (post-dilation aneurysm risk is greater)); TGA, transposition of the great arteries; TAPVR, total anomalous pulmonary venous return; ASD, atrial septal defect; PV, pulmonary valve

catheterization laboratory in ELBW infants. As majority of these infants are hemodynamically unstable requiring respiratory support, additional challenges are experienced by anesthesiologists during transcatheter occlusion.

There are several aspects of the sedation or anesthesia in neonates that must be considered in the cardiac catheterization lab. First, the cardiologists require physiologic variables as close to the normal values for the neonate as possible in order to make correct diagnoses regarding the heart defect. As a result, it is important that we provide enough anesthesia for the neonate for the investigation but not too much anesthesia to depress the myocardium. That anesthetics generally decrease cardiac contractility and disturb the balance of shunts in a dose-dependent manner should provide a metric for the amount of anesthetic that should be administered.

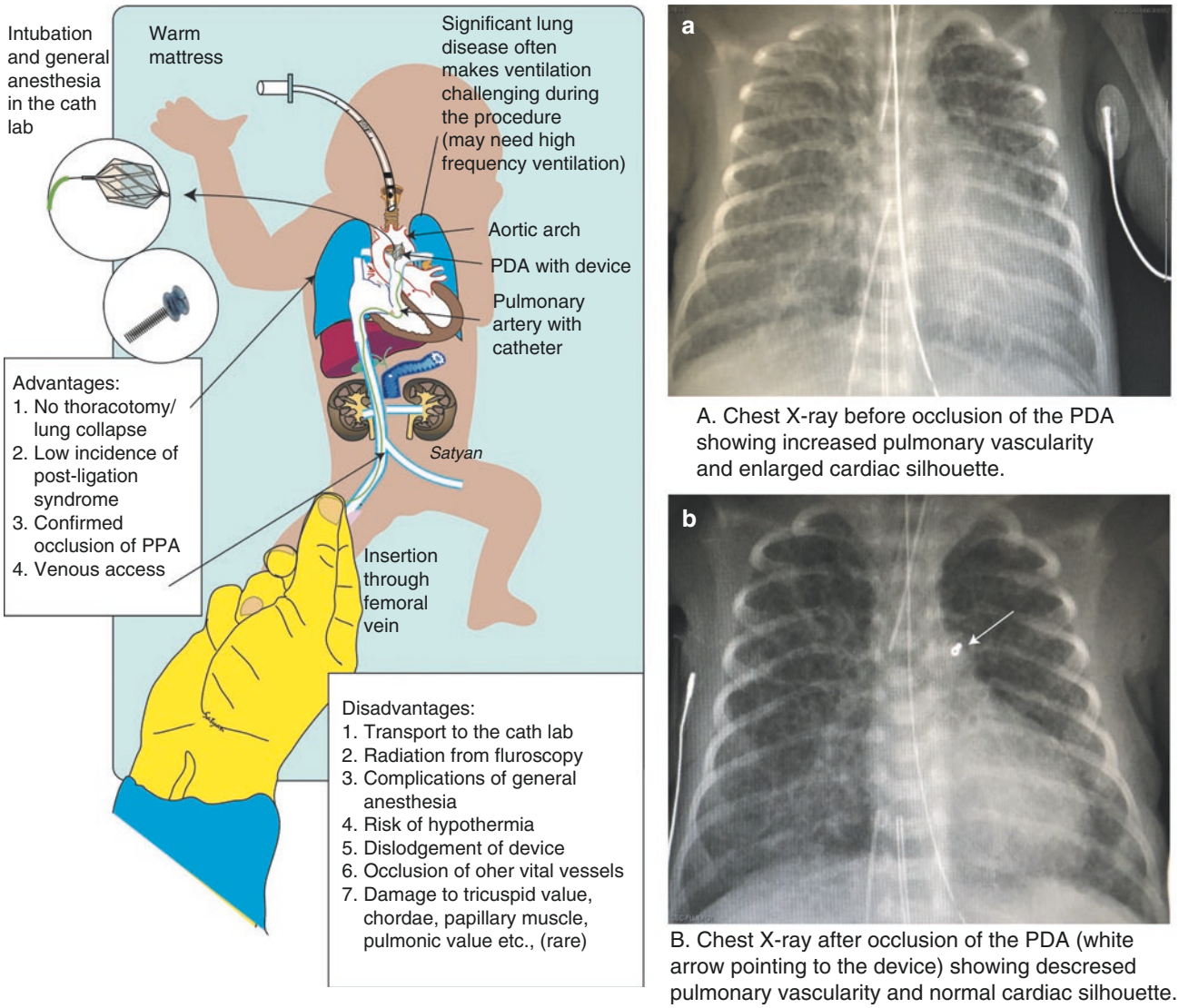

Fig. 13.9 Procedure for transcatheter occlusion of PDA in ELBW infants. The left panel shows the logistics of occlusion along with procedural challenges, advantages, and disadvantages. The right panel shows chest X-rays before (**a**) and after (**b**) transcatheter closure of PDA in a preterm infant showing reduction in pulmonary vascularity following the procedure (X-rays courtesy Dr. Frank Ing, Chief of Pediatric Cardiology, UC Davis Children's Hospital). Modified from Patent ductus arteriosus in preterm infants: is early transcatheter closure a paradigm shift? Vali P, Lakshminrusimha S, Pelech A, Underwood M, Ing F.J Perinatol. 2019 Nov;39(11):1449–1461. https://doi.org/10.1038/s41372-019-0506-7. Epub 2019 Sep 27. PMID: 31562396 Review. Copyright Satyan Lakshminrusimha

Hemodynamic measurements recorded during a diagnostic cardiac catheterization under general anesthesia may be discrepant from those estimated by the awake echocardiogram if excessive doses of anesthetics that depress the myocardium and vasodilate the peripheral vasculature are administered. Second, the anesthetics may alter the balance of SVR and PVR, thereby changing the amount and direction of shunted blood resulting in changes in the shunt fraction. This may be reflected in both the cardiac catheterization images and the SaO_2 measurements used to estimate the size of the shunt. Third, the anesthetics may decrease cardiac contractility or vasodilate the peripheral vasculature altering the pressure gradient across a narrowed cardiac valve or outflow tract, thereby raising doubts about whether or not to dilate the restricted orifice. If a balloon procedure is undertaken, significant changes in cardiac function may occur resulting in redistribution of blood flow that can cause complications especially in a critically ill neonate with limited cardiopulmonary reserve [148]. Most importantly, in the cardiac catheterization laboratory, access to the neonate is restricted by the presence of bulky radiological equipment requiring remote access to the IV injection ports and possibly obstructed views of the monitors by equipment and the dark lighting. Furthermore, if the anesthesiologist does not work in the cath lab frequently, the environment is unfamiliar and the nursing assistance may be variable. None of these issues may become important until an acute crisis occurs.

Cardiac arrhythmias are the most common major complication during pediatric cardiac catheterization procedures [149]. Cardiac arrhythmias occur in about 7% to 11% of cardiac catheterization procedures. They may be transient, but about 25% require cardioversion and about 40% antiarrhythmic therapy [150]. Often they are caused due to mechanical stimulation by the catheters. If they persist, then this could be due to myocardial ischemia, or damage to either the myocardium or the conduction system. Arrhythmias may be more likely if the child is hypoxic, hypercarbic, acidotic or has underlying electrolyte abnormalities. When antiarrhythmics or pacing is required, it is usually under the direction of the interventional pediatric cardiologist. Cardiac arrest has been reported to occur in about 2.5% of neonatal procedures in the catheterization lab.

Blood loss is infrequent during cardiac catheterizations (4–7%), but when procedures such as balloon dilatation are involved, the blood loss could be catastrophic [151]. In most centers, routine cardiac catheterizations do not involve much blood loss as the only vascular access occurs at the site of venous or arterial cannulation. Most cardiologists pay meticulous attention to stopping all bleeding once their catheters are positioned, but a minority does not, especially in cyanotic heart lesions that rely upon a higher hemoglobin for normal oxygen delivery. Careful attention to blood loss is particularly important in neonates who have a small blood volume and in cyanotic patients accustomed to an increased hematocrit [150]. When the latter cardiologists are involved, 1–2 units of PRBC should be present in the catheterization lab before commencing the procedure. Blood must always be present for balloon dilatations as a ruptured major vessel or dissection of a vessel may occur. The transfusion rate for interventional cases in one multicenter study (all-age children) was 14% [151]. It is wise to check the units to be certain the bags have been assigned to the neonate under your care, although most blood release for this purpose is type O negative.

Procedural damage to the cardiac endothelium could cause thrombus formation resulting in embolic complications. Heparin is frequently used (50–100 units/kg) to achieve an ACT of ≥200. There is a hemorrhage risk exists if the ACT is too high or as a result of any mechanical injury. Hypotension can be multifactorial; anesthesia related, hypovolemia due to unrecognized bleeding or due to cardiac complications. During the balloon inflation phase of valvuloplasty, there is a dramatic fall in cardiac output due to the transient very high afterload resulting in severe hypotension, which normally retunes to baseline with balloon deflation. If this hypotension persists, then concern for outflow tract rupture with tamponade or very severe valve regurgitation should exist, with emergent ultrasound and intervention accordingly [150].

There are important safety factors for the anesthesiologist when providing anesthesia in a fluoroscopy suite: the anesthesiologist should take the appropriate steps to avoid undue radiation exposure [146]. This should include wraparound lead aprons, thyroid protection, and protective eyewear. Also the use of portable lead shields between the radiation source and the anesthesia location is important. These considerations are especially pertinent when using biplane imaging as this increases the risk of exposure. Some anesthesiologists may wish to leave the room during the angiography runs; this obviously necessitates the ability to monitor the patient from a remote location, even for a short period. Also the anesthesiologist should use their personal dosimeter during all cases involving the potential for radiation exposure. Distance from source, degree of barrier protection, and exposure time (including the frequent screening imaging) are the important considerations. The threshold exposure for cataract formation can occur even after a few years of unprotected exposure. The maximum exposure for a medical worker is 5 rem/year.

Preanesthetic Assessment of the Neonate in the Cath Lab

The preanesthetic assessment of the neonate who is scheduled for cardiac catheterization lab procedures is exceedingly important in neonates. The history and physical examination should focus on the heart defect identifying limitations such as heart failure denoted by tachypnea, poor feeding, and recurrent URTI, which also may be due to

excess pulmonary blood flow. Details of every previous anesthetic and previous cardiac surgery and interventions are important to document. For example, the presence of a subclavian flap for coarctation repair requires that the NIBP and pulse oximetry probe should be sited on another extremity. These neonates often have a history of multiple previous admissions and procedures, which may make it difficult to establish IV access. Although drug allergies are infrequent in neonates, family history of reactions to anesthetics and polymorphisms in enzyme systems should be documented. The preoperative hematocrit may reflect systemic problems such as nutritional deficiency, feeding difficulties, chronic illness or chronic hypoxia, and repeated blood draws. If the HCT exceeds 65%, hyperviscosity may present difficulties and may require phlebotomy before commencing the procedure.

Anesthetic Technique

There is a host of different sedation and anesthesia regimens (Table 13.9) that have been used in neonates in the catheterization lab [152–159]. In many institutions, cardiac catheterization was historically performed using an oral [131, 152] or intramuscular sedation. Deep sedation with oral medications is unreliable in onset, efficacy, and duration. As a result, IM cocktails such as the Toronto cocktail and CM3 (meperidine, promethazine, and chlorpromazine) were more commonly used. However, this form of IM deep sedation is now rare due to the unpredictable nature of sedation, the slow emergence, and the risk of sterile abscess. More importantly, published reports [153, 154] of respiratory compromise and cardiac decompensation led to recommendations from the APA [155] against their use.

Neonates whose airways are already intubated are often sedated and ventilated by the NICU team using intermittent doses of midazolam and fentanyl and neuromuscular blocking agents. Although there are several theoretical benefits from maintaining spontaneous respiration during a diagnostic catheterization such as avoiding circulatory depression and avoiding the physiologic consequences of positive pressures within the chest. However, the risks of hypoventilation, atelectasis and desaturation, hypoxia, and cardiac arrest in critically ill neonates are too great to recommend this approach in most neonates and as such ventilation is usually controlled.

General inhalational anesthesia with tracheal intubation and paralysis (if needed) remains the most common anesthetic regimen for many neonates (Table 13.9). The incidence of respiratory and/or cardiac complications secondary to IV sedation in infants whose airways are not intubated is 5%. These adverse events during cardiac catheterization are more likely to occur in those infants with complex or cyanotic heart disease, young age, and reduced body weight. The incidence of airway complications is more likely in several subgroups of infants as listed in Table 13.10.

Intravenous sedation with propofol has been used for cardiac catheterization, although hypotension may present a concern at induction of anesthesia in premature infants who are hypovolemic. Ketamine is also a popular anesthetic because it maintains cardiac function (often despite hypovolemia), and side effects such as behavior problems do not occur in neonates [156, 157]. Its use is often combined with midazolam [158]. Pulmonary hypertension is associated with significant perioperative risk for complications in infants because it may cause a pulmonary hypertensive crisis and cardiac arrest. In adults, there is evidence that ketamine increases pulmonary artery pressures, although recent studies have disputed this notion [156, 159].

High-dose opioid anesthesia is considered the safest anesthetic technique for neonates with cardiac disease, but it may preclude tracheal extubation at the conclusion of the procedure. This is true for opioids such as fentanyl and sufentanil because of their prolonged half-lives. However, if the high-dose opioid technique were based on remifentanil, an opioid with a context-sensitive half-life of less than 5 min in neonates, then recovery will occur within minutes after terminating the remifentanil infusion, and the airway could be extubated immediately. Interestingly, some have maintained spontaneous respiration during remifentanil sedation (0.1–0.2 mcg/kg min) in infants for cardiac catheterization, although the dose required was quite variable and the need for supplemental sedation increased the risk of apnea [160, 161]. Remifentanil has also been administered in combination with an inhalational-based anesthetic in the cardiac catheterization lab [162], although the only pain that occurs is at the initial vascular access and if balloon dilatation is performed. We speculate that contribution of remifentanil

Table 13.9 Sedation techniques

1. Inhalational anesthesia
(a) Sevoflurane
(b) Isoflurane
(c) Desflurane
2. TIVA
(a) Propofol
(b) Ketamine
(c) Remifentanil
(d) Dexmedetomidine
3. Regional anesthesia: caudal/epidural or spinal

Table 13.10 Risk factors for airway events

Sedation
Airway abnormalities
GERD (gastroesophageal reflux disease)
High PVR
IJ/SCV access
Prostaglandin infusion
Down syndrome

may be more for its sedative effects than analgesia. In this situation, remifentanil may be used more for its sedative rather than analgesic effect. Interestingly, glycopyrrolate was needed to prevent bradycardia in these infants; also the hemodynamic assessment of these neonates will be closer to baseline if the heart rate is closer to normal, rather than slowed due to anesthesia.

Dexmedetomidine, an alpha-2 agonist, has been advocated for cardiac catheterization both as a solo anesthetic [163] and as an adjunct to inhalational or IV sedation regimen [164]. It has been used safely in neonates when combined with sevoflurane for surgical procedures [165]. Although dexmedetomidine may transiently increase systemic blood pressure and systemic vascular resistance (the loading dose) in those with pulmonary hypertension, PVR remained unchanged [166].

Some have advocated spinal anesthesia with hyperbaric 0.5% bupivacaine 1 mg/kg for infants undergoing cardiac catheterization [167], although the failure rate was 25%, and supplemental IV sedation was required in 50% of the infants. The potential benefits of this technique include stable hemodynamics, a reduced BIS without adding sedatives and avoiding the need to intubate the trachea in infants who could be at increased risk for extubation failure, and prolonged post-procedural ventilation due to chronic respiratory disease [168]. However, if a spinal technique were selected to prevent postoperative apneas in an ex-premature infant undergoing cardiac catheterization, the frequent need of adjunctive sedatives would result in an incidence of apnea no different from that of a general anesthetic [158, 169].

Although electrophysiology (EP) studies in neonates are infrequent, they may be performed for pharmacologically resistant tachyarrhythmias [170]. As a result of the complex nature of these procedures and the concern regarding the safety of prolonged deep sedation, general anesthesia is often required. A study of EP cases in adults questioned the safety of deep sedation because of the substantial (40%) risk of airway complications [171]; however, comparable data in neonates have not been forthcoming.

Several anesthetic regimens may be used to anesthetize neonates for EP cases [172]. However, it is best to avoid anesthetics that inhibit the sympathetic nervous system, such as dexmedetomidine, to minimize the risk of interfering with the detection and treatment of the arrhythmias. Total intravenous anesthesia with continuous infusions of propofol and remifentanil has been effective in this situation. Inhalational anesthetic may also be used; however, a rapid increase in the inspired concentration of desflurane in the absence of a background of opioids may induce paroxysmal sympathetic stimulation, although this has never been documented in a neonate. Sevoflurane maintains a stable heart rate and myocardial contractility in children with congenital heart defects [169]. All three inhalational anesthetics, isoflurane, desflurane, and sevoflurane, prolonged the QT interval without increasing the dispersion of repolarization and, therefore, without increasing the risk of torsades. The clinical significance of this last effect in the presence of an intrinsic myocardial conduction defect remains unclear. In cases in which the neonate is hemodynamically unstable or the arrhythmias are potentially life-threatening, invasive arterial pressure monitoring may be indicated.

Complications

Complications from cardiac catheter procedures have been reviewed in some detail in the literature [151, 170, 171, 173–177]. The overall incidence of all complications during interventional procedures (10%) was almost twice that for diagnostic procedures [143] with airway complications comprising 3% of the complications. When the risk of complications after cardiac catheterization was stratified by age, the risk in infants was twice that in older children [151, 175]. Other risk factors included low weight and cyanotic or complex congenital heart disease [176].

Interventional procedures have additional potential complications related to the anatomy and the procedure. Complications from balloon atrial septostomy include transient arrhythmias with premature ventricular contractions, supraventricular tachycardia, and atrial fibrillation, the most common. Partial/complete heart block and ventricular tachycardia may also occur. Failure to create an adequately sized atrial communication, perforation, or damage to the intracardiac valve has also been reported. Balloon dilation of the pulmonary valve is one of the most common interventional cardiac catheter procedures in infants, indicated for a pulmonary valve gradient >50 mmHg. These infants are usually receiving prostaglandin E1 (PGE1) infusions to maintain ductal patency. As a result of the respiratory depressant effects of the PGE1, these infants often require tracheal intubation. Aortic valve dilation has similar but greater risks than pulmonary valve dilation, most notably attributed to the risk of ventricular fibrillation from which resuscitation may be a challenge. Young infants may be at greater risk for complications from catheter-based therapies [151], although the risk is probably less than that of the surgical approach. In some cases, this allows a palliative procedure to be performed before a safer definitive repair can be undertaken, when the child has grown.

Pulmonary arterial hypertension (PAH) can lead to significant cardiac dysfunction and is known to place the infant at an increased risk of perioperative cardiovascular complications. Baseline suprasystemic PAH is a significant predictor of major complications [177]. Children with suprasystemic PAH have a significant risk of major perioperative complications, including cardiac arrest and pulmonary hypertensive crisis.

Rarely, the wire or catheter perforates a wall in the heart or a major blood vessel or the balloon ruptures a major valve or artery during a controlled dilatation. This potential disaster is best managed by increasing the inspired oxygen concentration to 100%, calling the cardiac surgery team for possible emergency bypass, stopping the procedure, and leaving the perforating wire/catheter in place or the balloon inflated. Blood should be available in the room to transfuse if bleeding persists. If the femoral venous catheter is involved in the perforation, a second large bore IV should be accessed for transfusion of blood products. A blood warmer should be placed in-line to warm the blood during transfusion. If surgery is required, additional blood should be ordered and a transport monitor and stretcher prepared for the rapid transfer to the OR. The severity of the perforation or accumulation of pericardial blood should be assessed using transthoracic echocardiography before transfer. If a hemopericardium is forming, pericardiocentesis should be performed immediately to preclude a cardiac tamponade.

There are several cardiac diagnoses that appear to have a high risk of mortality during cardiac catheterization. These include a stage 1 palliation of hypoplastic left heart syndrome; induction instability is associated with procedures performed prior to Glenn procedure. Single ventricle physiology with anesthesia induction and positive pressure ventilation has been reported to increase the risk of myocardial ischemia and cardiac arrest. Also pulmonary hypertension with RVH during the induction of anesthesia with positive pressure ventilation, decreases the right ventricular preload and increases the afterload. Due to a lack of pulmonary blood flow, resuscitation is extremely difficult. This necessitates maintaining an adequate preload along with inotropic support for the failing right ventricle. Inhaled nitric oxide should be readily available to reduce the afterload if either a pulmonary hypertensive crisis or cardiac arrest occurs.

In some institutions, all pediatric cardiac catheterization procedures are anesthetized by the members of the pediatric cardiac anesthesiology team. However, this may not always be possible. Those providing anesthesia care for neonates in the cardiac catheterization lab should be well acquainted with concepts of neonatal anesthesia, routine and complex congenital cardiac lesions, and the procedure site.

Interventional Radiology for Neuroimaging

Cerebral angiography is the most common neuro-interventional procedure for pediatric patients. CT and MRI scans are used more frequently now; however, the angiogram is still the gold standard and also allows intervention if necessary. Indications for angiography may include stroke, hemorrhage, vasculopathies, and AV malformations. These scans are best performed with a patient that lies still and can breath-hold as needed. In young children, this usually requires general anesthesia with intubation [146]. Removal of the femoral sheath can result in bleeding, especially if the patient will not lie still. Deep extubation or the use of dexmedetomidine post-extubation has been recommended; however, an appropriate location for prolonged monitoring of the sedated child is required. Blood pressure monitoring and control may also be necessary both during and post-procedure; this may require the placement of an arterial line. Postoperative management may be best provided in an intensive care setting. This allows for sedation as needed, appropriate hemodynamic monitoring and intervention as necessary, and hourly neurological assessments in the cases of interventional procedures.

Conclusion

The provision of anesthesia in the NICU and in medical units for neonates can be a daunting challenge. These infants are usually among the most critically ill neonates we are asked to anesthetize, often requiring major surgery and with substantive mortality rates. Practicing in an unfamiliar environment without access to the usual anesthesia equipment requires that the anesthesiologist be proactive in deciding what is required to successfully manage the infant. Furthermore, the NICU is often remote from the OR, rendering the anesthesiologist a virtual "solo" practitioner as assistance from other anesthesiologists and anesthesia technicians may be delayed or completely unavailable, such as at night. Restricted access to the infant and the use of unfamiliar ventilation modes and monitors also make care more difficult. The anesthetic prescription is usually relatively straightforward with most reports using an opioid-relaxant technique. It is very important to establish excellent communication between all the physicians and healthcare staff involved in the case. The anesthesiologist should use the knowledge and skills of the NICU staff including the physicians, nurses, and respiratory therapists to ensure the anesthetic proceeds smoothly. This will help to overcome potential difficulties that can arise during anesthesia in remote and unfamiliar locations. Teamwork and planning are of paramount importance in order to deliver safe, optimal care for these very ill neonates.

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Fetal Surgery and the EXIT Procedure

14

Marla B. Ferschl and Mark D. Rollins

Introduction

The goal of fetal surgery is to correct or mitigate a severe or otherwise potentially lethal congenital anomaly in utero to minimize the physiologic derangements caused by the lesion postnatally [1]. The subspecialty of fetal surgery has evolved significantly since the first fetal procedure, an intrauterine blood transfusion that was performed in 1963 [2]. Though some fetal procedures remain investigational, prospective trials have validated the efficacy of others, leading to an increased number of fetal procedures being performed worldwide. When providing perioperative care for these procedures, the anesthesiologist must treat two patients—the mother and the fetus. In this chapter, we evaluate the preoperative management of fetal surgical candidates with a review of maternal and fetal physiology, discuss the anesthetic techniques for both minimally invasive and open fetal procedures, detail postoperative pain management considerations, review fetal anomalies amenable for prenatal intervention, and examine the indications for the ex utero intrapartum therapy (EXIT) procedure with a focus on anesthetic management for EXIT cases.

Anesthetic Considerations for Fetal Surgery

Preoperative Evaluation of the Fetal Surgery Patient

Fetal procedures are indicated when an in utero intervention will alter the course of the pathologic process and prevent or mitigate otherwise predicable end-organ damage. International multidisciplinary guidelines for performing fetal procedures were originally established in 1982 [3]. In the intervening period, these recommendations have evolved and presently include the following: (1) the fetal diagnosis is accurately established; (2) the anomaly progression is predictable; (3) additional severe anomalies are not concurrently present; (4) if untreated, the anomaly would lead to fetal demise, end-organ damage, or severe morbidity; (5) maternal risk is low; (6) animal models have demonstrated success with in utero lesion treatment; and (7) interventions are performed at centers with specialized, multidisciplinary fetal teams, including access to bioethical care and counseling [4]. Improvements in imaging including ultrasound image resolution and the initiation of fetal magnetic resonance imaging (MRI) as a method of evaluating fetal anatomy have vastly improved the field of fetal therapy, allowing providers to develop therapeutic interventions for earlier gestational ages [5]. Lesions presently amenable to fetal intervention are listed in Table 14.1.

Planning for fetal surgery involves a multidisciplinary team that consists of surgeons, anesthesiologists, ultrasonographers, neonatologists, maternal-fetal medicine specialists, nurses, genetic counselors, and social workers. Anesthesiologists are a critical component of this perioperative process, especially the preoperative assessment of maternal health.

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Table 14.1 Fetal conditions amenable to prenatal intervention

Lesion	Intervention	Rationale
Fetal anemia	Fetal IUT	Prevent hydrops
TRAP	Radiofrequency ablation of acardiac twin	Prevent heart failure in viable twin
TTTS	Selective fetoscopic laser photocoagulation	Decrease unequal blood sharing between twins; prevent cardiac failure and hydrops
Amniotic band syndrome	Fetoscopic band ablation	Prevent limb loss
LUTO	Vesicoamniotic shunt placement or ablation of posterior urethral valves	Improve renal function and lung growth
Aortic stenosis with evolving HLHS	Balloon dilation of aortic valve	Increase blood flow through left ventricular outflow tract; increase likelihood of biventricular outcome
CDH	Fetoscopic tracheal balloon occlusion	Reduce pulmonary hypoplasia
SCT	Ablation of tumor vasculature or open debulking	Reduce high-output cardiac failure and fetal hydrops
CPAM	Thoracoamniotic shunting or open resection	Reduce hydrops, cardiac failure, and lung hypoplasia
MMC	Open or fetoscopic MMC repair	Reduce hindbrain herniation, hydrocephalus, and need for ventriculoperitoneal shunting; improve neurologic function

At no time should maternal safety be significantly jeopardized for a fetal intervention. Maternal risks, benefits, and alternatives should be thoroughly explained, focusing on possible outcomes from the proposed procedure and implications for both present and future pregnancies [6, 7]. Effective counseling is specific, thorough, realistic, and empathetic [8, 9]. If surgery proceeds for a fetus that is of a viable gestational age, additional discussion is necessary to determine whether resuscitation is advisable or possible in the event of fetal distress requiring emergent delivery.

Maternal Physiology

During pregnancy, women undergo significant physiologic changes that directly impact the perioperative anesthetic management [10–12]. These alterations are secondary to hormonal activity, increasing metabolic demands and biochemical changes from the growing fetus, placenta, and uterus. The physiologic changes of pregnancy at term are summarized in Table 14.2.

Maternal Circulatory System

Physiologic anemia during pregnancy (hemoglobin levels decreasing to 11 g/dL) may be attributed to a greater increase in plasma volume (50%) than red blood cell mass (25%) by term. The concentrations of albumin (25%) and total protein (10%) are reduced at term, with a corresponding decrease in colloid osmotic pressure of 5 mmHg [13].

Supine hypotension occurs during pregnancy from compression of the vena cava by the gravid uterus. In the supine position, aortic compression occurs in 15–20% of term pregnant women. Vena cava compression is nearly universal and may occur as early as the start of the second trimester. Vena cava compression causes venous blood to pool in the lower extremities and increases the risk of deep vein thrombosis.

Table 14.2 Cardiopulmonary changes of pregnancy

Component	Term value compared to prepregnancy
Cardiovascular	
Cardiac output	Increased 40–50%
Stroke volume	Increased 25–30%
Heart rate	Increased 15–25%
Intravascular volume	Increased 35–45%
Plasma volume	Increased 45–55%
Erythrocyte volume	Increased 20–30%
Coagulation factors	
Factors I, VII, VIII, IX, X, XII, VWF	Increased
Factors XI, XIII, antithrombin III, protein S	Decreased
Factors II, V, protein C	Unchanged
Pulmonary	
Minute ventilation	Increased 45–50%
Tidal volume	Increased 40–45%
Respiratory rate	Increased 0–15%
Oxygen consumption	Increased 20%
Total lung capacity	Decreased 0–5%
Vital capacity	No change
Functional residual capacity	Decreased 20%

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Increased peripheral sympathetic nervous system activity is a compensatory reflex that attenuates the severity of supine hypotension in the presence of aortocaval compression to maintain the blood pressure despite a reduced cardiac output. Sympathetic tone is reduced with general or neuraxial anesthesia, further increasing the degree of hypotension in the supine position. Consequently, displacing the uterus to the left by elevating the right hip or airplaning the table to the left, along with administering fluids and vasopressors during

anesthesia after mid-gestation, will increase the maternal preload, cardiac output, and blood pressure.

Cardiac output increases during pregnancy to a value 40–50% greater than the prepregnancy by the third trimester. The increased cardiac output ensures the total oxygen delivery is maintained despite the reduced oxygen-carrying capacity secondary to physiologic anemia. The greatest increase in cardiac output occurs immediately after delivery, which may reach ≥80% greater than the antepartum levels. The sources of the increased cardiac output include autotransfusion from the uterus, removal of aortocaval compression, and diminished lower extremity venous pressure.

Pregnancy results in significant increases in factor I (fibrinogen) and factor VII, decreases in factors XI and XIII and antithrombin III, and smaller increases in other factors (Table 14.2). These changes result in a hypercoagulable state with a 20% decrease in both prothrombin time (PT) and partial thromboplastin time (PTT). In most cases, platelet levels decrease minimally (10%) by term because of plasma dilution. Up to 10% of pregnancies are complicated by thrombocytopenia with gestational thrombocytopenia accounting for approximately 70% of cases [14].

Maternal Airway and Pulmonary Systems

During pregnancy, edema and tissue friability increase throughout the larynx, pharynx, and trachea. This poses difficulty for laryngoscopy and intubation. The presence of preeclampsia, respiratory infections, and labor also increase airway edema. The present rate of failed peripartum intubation is estimated to be approximately 1:533, based on a multi-institutional database [15].

Maternal minute ventilation increases approximately 50%, oxygen consumption increases by more than 20%, and functional residual capacity decreases by 20% at term. These changes result in rapid desaturation during apnea and increase the risk of complications when combined with difficult intubation. The increased minute ventilation decreases the maternal $PaCO_2$ to 30 mmHg by the end of the first trimester. The increase in excretion of renal bicarbonate (HCO3, 20–21 mEq/L) leads to a slightly alkalotic arterial pH, at 7.42–7.44.

Other Maternal Physiologic Changes

During pregnancy, the esophageal sphincter tone is reduced, gastric pH is decreased, and gastric pressure is increased from the gravid uterus. These changes increase the frequency of acid reflux during pregnancy and the risk of aspiration of gastric contents as general anesthesia is induced [16]. Administration of nonparticulate antacids, H_2 receptor antagonists, and/or metoclopramide for aspiration prophylaxis should be considered before surgical procedures during pregnancy [17].

Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and bilirubin levels increase to the upper limits of normal during pregnancy. As the plasma protein concentrations decrease, the free serum concentrations of highly protein-bound maternally administered drugs increase.

Renal blood flow and glomerular filtration rate increase 50–60% by the start of the second trimester of pregnancy. Consequently, blood urea nitrogen and serum creatinine values decrease approximately 50% during pregnancy.

The minimum alveolar concentration (MAC) for inhalational anesthetics decreases during pregnancy. This is based on studies in which pregnancy decreased the MAC in animals by 40% and in humans by 28% during the first trimester [10, 11, 18, 19]. However, an EEG study of the effects of sevoflurane suggests that the anesthetic effects on the brain in pregnant and nonpregnant patients may not differ [20]. Given these findings, it is not recommended to reduce standard anesthetic levels in stable obstetric patients.

Uterine and Placental Physiology

Physiologic transfer of gases, nutrients, and drugs between mother and fetus occurs via the placenta. Maternal blood flows from the uterine spiral arteries into the intervillous space which lies between the basal and chorionic placental plates (Fig. 14.1). Fetal blood flows to the placenta via two umbilical arteries. After placental transfer at the chorionic villi, oxygen and nutrients return to the fetus through the umbilical vein.

Uterine blood flow increases from approximately 100 mL/min before pregnancy to approximately 700 mL/min (10% of cardiac output) by term. Approximately 80% of uterine blood flow perfuses the placenta, and 20% maintains the myometrium. Uterine vessels remain nearly maximally dilated during pregnancy. Maternal hypotension and decreased cardiac output can reduce uterine blood flow and result in placental hypoperfusion, fetal hypoxemia, and fetal acidosis. Maternal heart rate correlates closely with cardiac output during pregnancy [21, 22]. Consequently, present recommendations for cesarean delivery are to maintain both maternal blood pressure and heart rate near baseline to optimize the fetal condition before delivery [22]. These recommendations should also be strongly considered during fetal surgery. Methods to achieve these goals include the use of colloid preload or crystalloid co-load with initiation of anesthesia, a prophylactic alpha-agonist (e.g., phenylephrine) infusion titrated as needed, and the use of left uterine displacement [22].

Fetal Physiology

Fetal surgery can disrupt both uteroplacental and fetoplacental hemodynamics and gas exchange. An appropriate understanding of fetal physiology is essential to ensure fetal

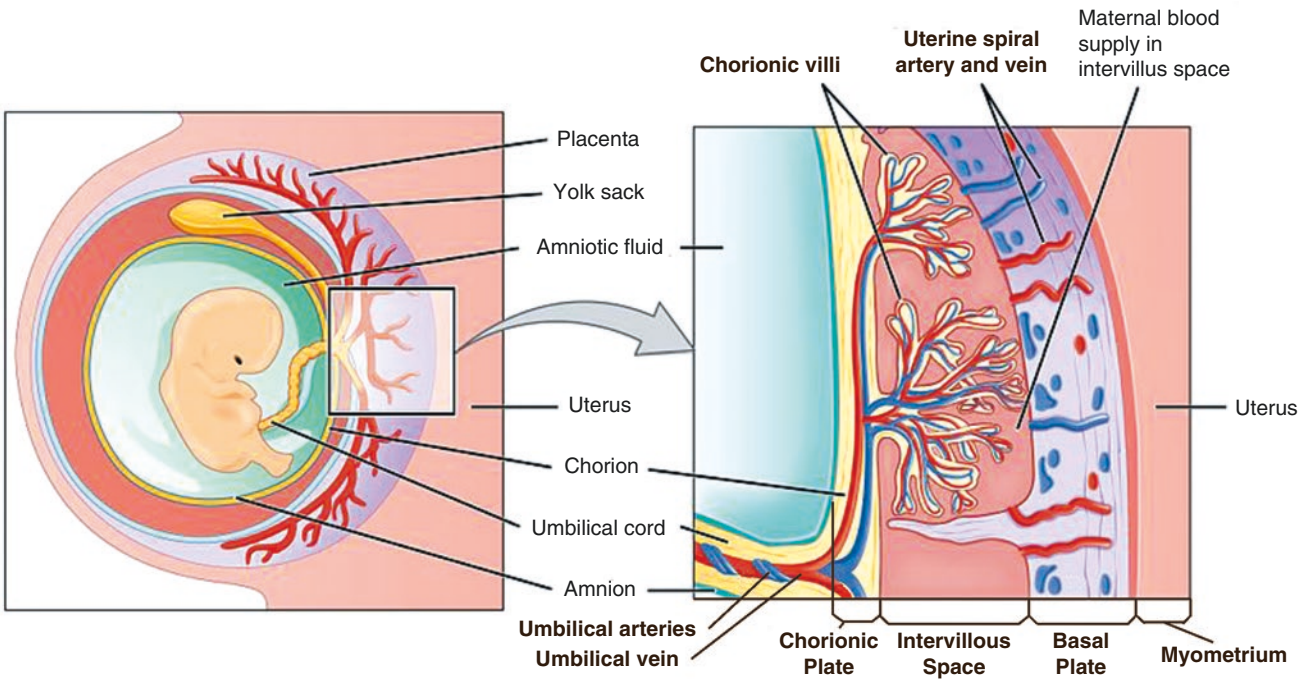

Fig. 14.1 Placenta anatomy. Depiction of the placenta showing the structure and components of both fetal and maternal circulation. Figure modified from original on Wikimedia Commons. Author OpenStax College. https://commons.wikimedia.org/wiki/File:2910_The_Placenta-02.jpg

well-being. Fetal hemoglobin, which binds oxygen with greater affinity than adult hemoglobin to compensate for the relative hypoxemia, is the primary oxygen carrier, although the production of adult hemoglobin begins at approximately 32 weeks' gestation [23]. Fetal hemoglobin is relatively left-shifted on the hemoglobin oxygen dissociation curve resulting in 50% saturation (P50) at 18 mmHg compared with an adult hemoglobin P50 of 27 mmHg. Fetal acidosis promotes oxygen off-loading in times of distress [24]. With pregnancy, the maternal hemoglobin is relatively right-shifted with a P50 of 30 mmHg, which facilitates the transfer of oxygen from the mother to the fetus. Fetal hemoglobin levels increase linearly throughout gestation, with a level of approximately 11 g/dL at 17 weeks to 18 g/dL at term [25].

Two-thirds of circulating fetal blood is within the placenta. After the first trimester, fetoplacental blood volume corresponds to gestational age and fetal weight with typical values of 100 to 160 mL/kg [25, 26].

Fetal PaO_2 is normally 20–40 mmHg [24]. However, if the mother inspires 100% oxygen, fetal PaO_2 may increase to 60 mmHg. Fetal hemoglobin usually remains <65% saturation because a significant amount of oxygen is extracted from the maternal blood before it reaches the placenta [27, 28]. In the presence of non-reassuring FHR patterns, supplemental oxygen for the mother improves fetal oxygenation during labor (based on fetal pulse oximetry) [29] and is likely beneficial during fetal surgery, although this is not evidence-based [30].

All medications transfer from the mother to the fetus to some degree, but some are significantly limited. Molecules that are large, ionized, lipid insoluble, or significantly protein bound do not readily cross the placenta. For example, succinylcholine, non-depolarizing neuromuscular blockers, heparin, and glycopyrrolate do not cross the placenta to a significant degree. Other anesthetic agents such as opioids and inhalational anesthetics readily cross from the maternal to fetal circulation. Sugammadex transfers, although its safety in terms of fetal exposure and effect on the pregnancy remains unknown. Presently, it is not recommended for use during pregnancy.

Fetal circulation is significantly different from the circulation of the neonate (Fig. 14.2). Oxygenated blood from the placenta travels to the fetal liver via the umbilical vein (saturation 70–80%) [31]. From the liver, blood enters the inferior vena cava by one of two routes: either via the portal sinus circulation or the ductus venosus. Blood is then preferentially directed to the fetal brain (carotid arteries) and heart (coronary arteries) via the foramen ovale. Deoxygenated fetal blood reaches the placenta via two umbilical arteries.

Normal fetal cardiac output is in the range of 425 to 550 mL/min/kg throughout pregnancy [32]. Heart rate is the primary determinant of fetal cardiac output, as fluid-filled lungs and decreased myocardial contractility prevent preload from affecting cardiac output to any great extent [24, 33]. Sudden or significant decreases in fetal heart rate reduce fetal cardiac output and lead to fetal distress. Fetal lungs pro-

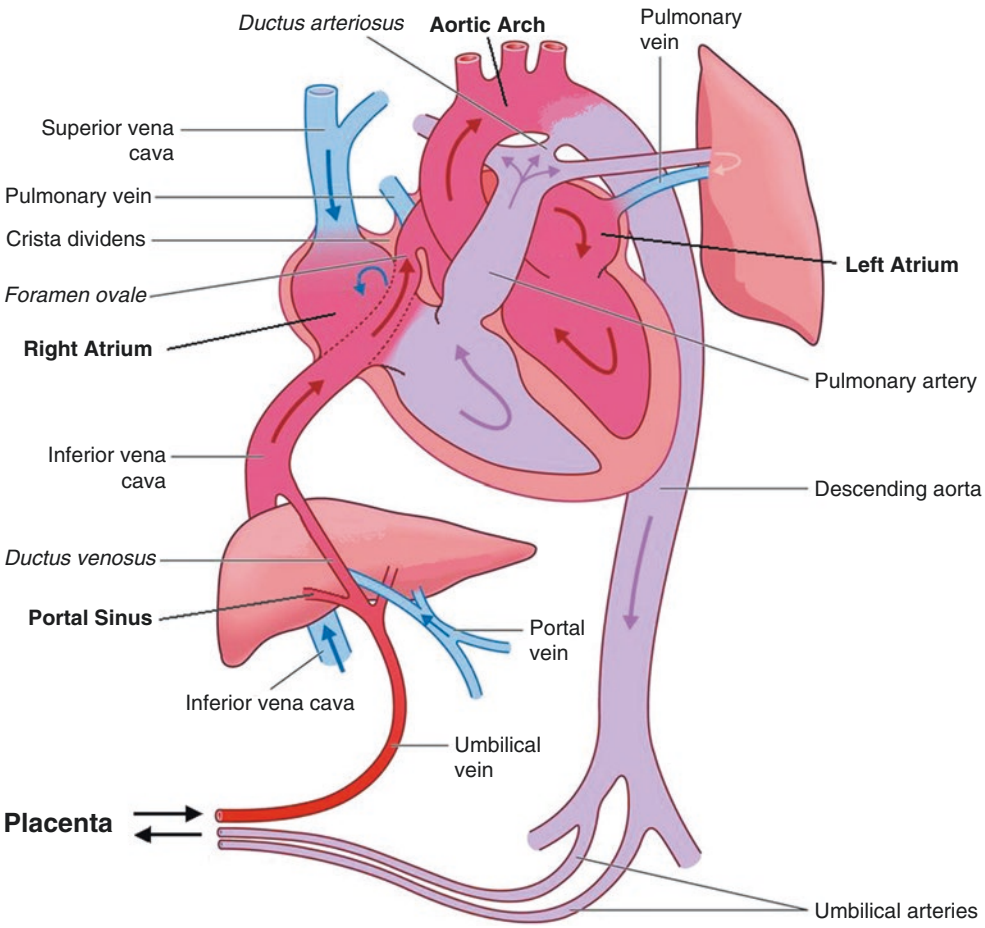

Fig. 14.2 Fetal circulation. Fetal circulation allows oxygen-rich blood from the placenta to flow to the liver where it divides into either the portal sinus or ductus venosus before entering the inferior vena cava. The majority of flow passes through the foramen ovale and enters the aorta (directly perfusing the brain and heart). Deoxygenated blood returns to the placenta via umbilical arteries. Figure modified from Murphy JP. The fetal circulation. Continuing Education in Anaesthesia Critical Care & Pain, Volume 5, Issue 4, 1 August 2005, Pages 107–112

duce 100 mL/kg/day of fluid that flows from the trachea and is either swallowed or enters the amniotic cavity.

Fetal hepatic synthetic and metabolic functions improve throughout gestation. Most drugs that cross the placenta into the fetal circulation still undergo first-pass metabolism before reaching the fetal brain or heart [34]. Coagulation factors are synthesized independent of the maternal circulation and increase in concentration with gestational age, though clot formation is immature until about 6 months after birth. Platelet production commences at 5 weeks' gestation and increases to the normal adult range by 22 weeks' gestation [35, 36].

Certain procedures can significantly affect the hemodynamics in the fetus. Perturbations in maternal physiology such as hypotension, hypocarbia, or uterine contractions all decrease uteroplacental blood flow, which can lead to fetal distress. Umbilical cord compression and direct fetal compression can impact the fetal blood flow. Intraoperative fetal monitoring via direct ultrasonographic assessment of umbilical blood flow and fetal echocardiography are recommended during fetal procedures. These monitors assess the fetal heart rate, cardiac contractility, and cardiac filling, as well as allow for Doppler flow assessment in the ductus arteriosus and umbilical artery. Absent and reversed umbilical artery flow is associated with increased rates of fetal demise [37]. For open procedures, when fetal hemodynamic instability is anticipated (e.g., open sacrococcygeal teratoma (SCT) resections, EXIT procedures), fetal pulse oximetry can be employed.

If fetal distress occurs during fetal surgery, the anesthesiologist should optimize maternal hemodynamics and fetal perfusion. This includes augmenting maternal blood pressure and cardiac output, ensuring adequate uterine relaxation, and altering the maternal position to optimize venous return (left uterine displacement). The surgical team should be alerted to ensure that the umbilical cord flow is not compromised and that fetal manipulation and position have not contributed to the distress. A decrease in the body temperature of the fetus can also cause bradycardia [38, 39]. Strategies should be undertaken to prevent fetal hypothermia by maintaining maternal core temperature with a warming device and, in the case of open surgery, ensuring that irrigation fluids are warmed and the temperature of the amniotic cavity is monitored.

Fetal Pain Perception

As early as 18 weeks' gestation, the fetus can mount a sympathetic stress response to noxious stimuli such as pain [40, 41]. However, the ability of the fetus to perceive pain remains controversial, as the stress response is mediated at the level of the spinal cord, brain stem, and/or basal ganglia and is unlikely to correlate with conscious perception of pain, which is mediated by the cortex [42, 43]. However, fetal administration of opioid medications blunts the fetal stress response [40], and in preterm neonates, diminishing the stress response to surgery improves outcomes [44, 45]. Although inhalational anesthetics readily pass from the maternal to the fetal circulation, they do not provide significant analgesia or reliably suppress autonomic reflexes in the fetus [46]. Opioids are required to reliably blunt the stress response in the fetus.

Peripheral sensory nociceptors in the skin develop between 10 and 17 weeks' gestation [47], and a fetus can reflexively withdraw from a painful stimulus by 19 weeks' gestation, without cortical input [48, 49]. However, pain perception requires intact neural pathways from the spinal cord to the primary sensory cortex and on to higher cortical structures. As a result, fetuses are unlikely to perceive pain before 24 weeks' gestation [49]. This theory is supported by cortical EEG activity, which is present only 2% of the time in 24-week fetuses but 80% of the time in fetuses that are 34 weeks' gestation [50].

Because the exact timeline of pain perception by the fetus is unknown, and because blunting the neural-humoral response associated with procedures in the fetus is beneficial, analgesia should be provided during surgery in the fetus [51]. Analgesia has been administered safely to fetuses for over 35 years. In addition to blunting pain and the circulatory response to noxious stimuli, analgesia also promotes fetal immobility [52, 53].

Opioids reach the fetal circulation by direct fetal intramuscular injection or maternal administration. For most open fetal procedures that cause direct fetal stimulation, opioids are administered directly to the fetus intramuscularly. The typical regimen is fentanyl 10–20 mcg/kg, administered under direct visualization or ultrasound guidance before the hysterotomy, although equipotent doses of alternate opioids can be used [53, 54]. In addition to opioids, many centers combine prophylactic anticholinergic medication (atropine 20 mcg/kg) as well as a muscle relaxant (e.g., rocuronium 2.5 mg/kg or vecuronium 0.25 mg/kg) into a single injection that is administered to the fetus [52, 55]. The onset of muscle relaxation in the fetus usually occurs within 5 min and lasts 1–2 h [56].

In addition to directly administered medication to the fetus, maternally administered anesthetic agents cross the placenta and affect the fetus. Remifentanil, 0.1 mcg/kg/min, crosses the placenta and provides adequate fetal immobility for fetoscopic procedures on the umbilical cord or the placenta [57]. Inhalational anesthetic agents also cross the placenta quickly, with studies in cesarean sections indicating that isoflurane has a fetal-to-maternal ratio of 0.7 after only 10 min [58]. However, large doses of inhalational anesthetics may depress the fetal myocardium, leading to fetal acidosis [59, 60]. As a result, some institutions augment inhalation-based anesthetic regimens with remifentanil [61] or a combination of remifentanil and propofol to decrease the amount of inhalational anesthetic administered to the mother [62].

Anesthetic Neurotoxicity

The impact of anesthetic agents on the development of the human brain is of foremost concern to providers administering anesthetic agents to fetuses and neonates (see also Chap. 18). Animal models demonstrated profound histologic changes from anesthetic exposure to inhalational anesthetics, propofol, and benzodiazepines. Furthermore, learning and behavior deficits have been noted [63, 64]. Two recent human trials that examined the effect of a single, short-duration anesthetic exposure at a young age failed to demonstrate any substantive early neurodevelopmental consequences [65, 66]; the FDA withdrew its 2011 proscription of anesthesia in children less than 3 years of age undergoing elective procedures [67]. However, long-term and repeat exposure outcomes studies are ongoing. Based on animal evidence, the U.S. Food and Drug Administration advisory committee issued a warning in 2016 that "repeated or lengthy use of general anesthetic and sedation drugs during surgeries or procedures in children younger than 3 years or pregnant women during their third trimester may affect the development of children's brains." [67] To date, no clinical studies have examined the neurocognitive effects of mid-gestation fetal surgery, though an international registry has been created to assess long-term neurodevelopmental outcomes in fetuses exposed to anesthetic agents during fetal surgery (Clinical Trials.gov identifier NCT02591745) [68]. Data are confounded by the fact that some fetal anomalies associated with "in utero" procedures result in developmental delay independent of any exposure to anesthetics, and fetuses with congenital anomalies often require multiple anesthetics after birth [69].

Anesthetic Management for Minimally Invasive Fetal Procedures

Anesthesia for fetal procedures requires the same preoperative evaluation and planning process as non-obstetric surgery during pregnancy. Patients should be medically optimized,

appropriately fasted, and maintained in left uterine displacement for the duration of the procedure. For most minimally invasive fetal procedures, monitored anesthesia care with infiltration of local anesthetic is sufficient, with similar dependability to neuraxial techniques [70]. However, for procedures involving multiple fetoscopic insertion sites, or when maternal immobility is essential for the procedure, a neuraxial technique may be preferred. Except in the case of fetoscopic myelomeningocele (MMC) repair in which positioning the fetus as well as the possible need for uterine exteriorization may require maternal general anesthesia [71], most minimally invasive procedures do not require a general anesthetic. If immobility of the fetus is desired, it can be assured with direct administration of a muscle relaxant, as described previously. For minimally invasive procedures that directly involve the fetus (as opposed to the umbilical cord or the placenta), an opioid should be administered to the fetus in addition to the muscle relaxant. Resuscitation medications for the fetus including atropine (20 mcg/kg) and epinephrine (10 mcg/kg) should be prepared in single-dose aliquots and transferred to the surgical field in a sterile fashion before surgical incision. Should the fetus be of viable age and after all parties (mother and the perioperative team) are in agreement with the need for resuscitation, plans should be prepared for a possible emergent cesarean section under general anesthesia in the event of fetal distress. The anesthesiologist should be prepared for neonatal resuscitation and preoperative steroids previously administered to improve fetal lung maturity if there is concern for premature delivery. Intraoperative use of pressurized uterine crystalloid irrigation may lead to maternal pulmonary edema, and maternal intravenous fluid should be limited (<2 liters) to mitigate this risk [72].

Anesthetic Management for Open Fetal Surgery

Open fetal procedures are more complex than closed procedures as they involve a uterine hysterotomy and direct fetal manipulation, which is associated with greater potential for maternal and fetal hemodynamic instability, advanced fetal monitoring, and an increased risk of maternal complications. Providers must prepare for maternal and fetal resuscitation, blood transfusion, and emergent delivery (Table 14.3). In most instances, the mother requires general anesthesia. After tracheal intubation, anesthesia is maintained with an inhalational anesthetic to relax the uterus, as well as to provide general anesthesia for the mother and fetus. High-dose inhalational anesthesia has been historically used, although many fetal centers are transitioning to a supplemental intravenous anesthetic (SIVA) technique to reduce fetal cardiac dysfunction and umbilical artery flow abnormalities that have been reported with these concentrations of inhalational agents [73]. This hybrid technique combines 1–1.5 MAC of inhalational anesthetic with either an intravenous remifentanil infusion or the combination of two intravenous infusions, propofol and remifentanil [59, 62].

Table 14.3 Anesthetic approach for open fetal surgery

Initial visit
• Fetal evaluation to exclude other anomalies and determine extent of lesion, placental location, and estimated fetal weight.
• Maternal evaluation, including complete history and physical exam, multidisciplinary counseling, and plan for emergent delivery if fetus is viable.
Preoperative
• High lumbar epidural placement.
• Maternal blood typed, cross-matched, and immediately available.
• Fetal blood prepared and immediately available (type O-negative, leukocyte depleted, irradiated, cytomegalovirus negative, cross-matched against the mother).
• Weight-based fetal medications prepared and passed to scrub nurse in sterile unit doses.
• Maternal antacid and tocolytic (rectal indomethacin) administered.
• Presurgical multidisciplinary team meeting.
Intraoperative
• Maternal normothermia maintained with forced-air warming device.
• Sequential compression devices placed on lower extremities.
• Left uterine displacement.
• Preoxygenation followed by rapid sequence induction and intubation.
• Maintain maternal Fi02 > 50% and end-tidal CO2 28–32 mmHg.
• Large-bore intravenous access obtained; arterial line placed or immediately available.
• Maternal mean arterial pressure maintained within 10% of baseline with intravenous phenylephrine, ephedrine, and/or glycopyrrolate.
• High-dose volatile anesthetic agents (2–3 MAC) to relax uterus; alternatively, volatile anesthetic at 1.0–1.5 MAC with SIVA technique.
• Nitroglycerine prepared for administration in case of need to improve uterine relaxation.
• Administration of fetal muscle relaxant and opioid with or without anticholinergic agent. Fetal IV access can be obtained if significant fetal blood loss is anticipated.
• IV loading dose of magnesium sulfate for tocolysis.
• Maternal crystalloid limited to 2 liters to prevent pulmonary edema.
• Epidural activated with uterine closure for postoperative pain control.
• Extubate maternal trachea when fully awake.
Early postoperative
• Continue maternal tocolytic therapy.
• Maternal epidural analgesia for pain control.
• Monitor uterine activity and fetal heart rate.
• Operative team debrief.
• Plan for periodic fetal assessment and possible need for delivery.

Modified from reference 54

Before the mother enters the operating room, the multidisciplinary team should meet to discuss a perioperative plan for the fetal procedure. Blood for both the mother and fetus (O-negative, cytomegalovirus negative, irradiated, leukocyte reduced, maternally cross-matched) should be cross-matched and available. Weight-based unit-dose medications for the

fetus should be prepared including an opioid and a muscle relaxant (as detailed previously), in addition to resuscitation medications (i.e., atropine and epinephrine), and these should be transferred sterilely to the surgical field.

As in the case for all pregnant patients undergoing surgery, the patient should be fasted and given an antacid before anesthesia is induced. She should be positioned with left uterine displacement. A high lumbar epidural catheter is placed preoperatively to provide postoperative analgesia. Before induction of anesthesia, the well-being of the fetus should be verified using umbilical artery flow patterns (abnormal flow patterns may be an early sign of fetal distress) [73] as well as echocardiographic evaluation. Additional monitoring modalities for the fetus include assessing flow across the ductus arteriosus and periodic cardiac imaging to determine systolic function [59, 74, 75]. Monitoring should continue intermittently throughout the procedure to ensure adequate fetal well-being and assess the effect of maternal positioning, surgical procedure, and anesthetic technique on the fetus.

General anesthesia is induced via a rapid sequence technique to minimize the risk of aspiration. Maternal hemodynamics are closely monitored during induction to maintain the mean arterial pressure within 10% of baseline and the heart rate close to the baseline measurement [22].

Though maternal arterial lines are not always routinely placed, one arm should remain accessible intraoperatively in case line placement becomes necessary. Phenylephrine is the vasopressor of choice as it has been shown to improve fetal acid-base status [76], though boluses of glycopyrrolate or ephedrine can assist in maintaining maternal heart rate and cardiac output [21, 22, 77]. An additional large-bore intravenous catheter is placed for maternal resuscitation and possible rapid blood transfusion. Intravenous fluids should be limited to <2 liters to reduce the risk of maternal pulmonary edema associated with tocolytics [78]. The use of colloids can be considered to assist in maintaining maternal blood pressure and cardiac output while limiting overall fluid administration. Maternal ventilation is adjusted to maintain end-tidal carbon dioxide tensions in the normal range for pregnancy (28–32 mmHg).

Before skin incision, the concentration of inhalational anesthetic should be increased to 1.0–1.5 MAC with SIVA or to 2.0 MAC without SIVA. Adequate uterine relaxation is assessed surgically, with additional inhalational agent administered as needed, up to 3 MAC. If further uterine relaxation is required, it can be achieved with intravenous nitroglycerine in small bolus doses (100–200 mcg) or as an infusion. For those women in whom general anesthesia is contraindicated, a neuraxial technique with an intravenous infusion of nitroglycerine (up to 20 mcg/kg/min) may be required to adequately relax the uterus [79]. To date, no single anesthetic technique appears to be superior to any other.

Once the uterus is exposed, a small hysterotomy is made and extended with an absorbable lactomer stapler. The stapler seals the amniotic membranes to the endometrium and prevents hemorrhage from the relaxed uterine wall. Uterine blood loss during this part of the procedure can be abrupt, massive, and difficult to quantify. Blood products should be checked and readily available for transfusion. Amniotic fluid, which is lost upon violation of the uterine wall, is continuously replaced with warmed crystalloid solution, and intrauterine temperature is monitored to prevent fetal hypothermia and associated fetal distress [38, 39].

If the fetus is at risk for hemorrhaging during the surgery (e.g., SCT resection), intravenous access should be established in the fetus for volume resuscitation. Sterile microbore tubing can be primed, passed across the surgical field, and secured in a vein to facilitate administration of warmed fluids and medications to the fetus. In an emergency, the umbilical vein can be directly cannulated in the surgical field. In the unlikely event of a cardiopulmonary arrest in the mother, the fetus should be delivered after 4 min of unsuccessful maternal resuscitation to increase the efficacy of resuscitation and the possibility of maternal survival [80].

For tocolysis, a loading dose of magnesium sulfate (4 to 6 grams IV) is administered to the mother over 20 min, followed by an infusion of 1–2 g/h [81]. Typically, this is commenced after uterine closure, although at some fetal treatment centers, it is commenced before incising the uterus. After the bolus of magnesium, the concentration of inhalational anesthetic is decreased, and the epidural is initiated after a negative test dose. When surgery is completed, the trachea is extubated when the patient is awake.

Postoperative Considerations

Postoperative concerns specific to fetal surgery include the need for continued fetal monitoring and prevention of premature labor. Minimally invasive procedures rarely require tocolysis beyond an initial dose of indomethacin. After open fetal surgery, uterine contractions are common and are typically monitored for at least 2 days postoperatively. The magnesium infusion is usually continued for 24 h postoperatively, although it may require supplementation with additional agents such as indomethacin or nifedipine. Indomethacin use requires periodic echocardiographic evaluation of the fetus as it may lead to premature closure of the ductus arteriosus.

Postoperative pain control in the mother is normally achieved using systemic oral medications in the case of minimally invasive procedures and via an epidural catheter in the case of open procedures. Intravenous opioids can also be used, but large doses can decrease the variability of the fetal heart rate and make the fetal heart rate tracing difficult to interpret [82]. Inadequately controlled pain can increase oxytocin levels in the mother and result in preterm labor [83]. After open fetal surgery, mothers are at greater risk for preterm premature rupture of the membranes, preterm labor,

infection, and uterine rupture [84]. Antenatal steroids should be administered to improve fetal lung maturity. Fetal well-being is assessed by postoperative ultrasonography and heart rate monitoring, depending on age of the fetus and the plan for fetal distress. Fetal complications include intracranial hemorrhage, infection, heart failure, oligohydramnios, and demise. A cesarean section is required for the delivery of the present and all future pregnancies to mitigate the risk of uterine rupture.

Specific Fetal Conditions Amenable to Fetal Treatment

Fetal Anemia

Anemia in the fetus is a serious condition that may increase cardiac output, tissue hypoxia, lactic acidosis, fetal hydrops, and intrauterine demise. The most common cause of fetal anemia is due to maternal alloimmunization, which leads to hemolytic disease of the fetus and neonate. In this scenario, maternal IgG antibodies cross the placenta and cause fetal red blood cell hemolysis. Other causes of fetal anemia include parvovirus B19, fetomaternal hemorrhage, and inherited fetal anemias, such as homozygous alpha thalassemia and Blackfan-Diamond anemia. An increased peak middle cerebral artery blood flow velocity, measured on non-invasive Doppler studies of the fetus, suggests moderate to severe fetal anemia. Umbilical vein intrauterine transfusion (IUT) of type O, Rh-negative, irradiated, leukocyte-depleted, packed red blood cells that have been cross-matched with the mother treats fetal anemia in fetuses over 18 weeks' gestation [85]. The amount of blood transfused is calculated based on a formula that incorporates the initial fetal hematocrit (measured from the umbilical vein before transfusion), the hematocrit of the donor blood, and the estimated fetal-placental blood volume based on gestational age [86]. A post-procedure hematocrit of 45–55% is targeted, and IUTs are often repeated every 1–3 weeks to maintain an adequate hematocrit until the fetus can be delivered at term [85, 87].

IUT procedures are generally performed with ultrasound guidance under local anesthesia with minimal need for maternal sedation. Fetal movement can be prevented with the use of a muscle relaxant, either injected intramuscularly into the fetus or directly into the umbilical vein [88]. Although rare, if an intrahepatic approach for transfusion is chosen, fentanyl should also be administered to the fetus to ameliorate the fetal stress response [89].

Complications occur in approximately 3% of cases. The range of complications include accidental umbilical artery puncture leading to vasospasm, fetal volume overload, infection, and preterm rupture of the membranes. These can result in fetal distress that requires emergent cesarean delivery [90]. Fetal demise occurs in 2% of IUTs [90].

Twin Reversed Arterial Perfusion (TRAP) Sequence

TRAP sequence occurs in monozygotic twin or triplet pregnancies where one fetus is not attached to the placenta and instead is perfused in a retrograde fashion via vascular anastomoses from the second "donor" fetus. This pattern of perfusion results in a nonviable, acardiac, acephalic fetus, whereas the donor twin is at risk for high-output heart failure, hydrops fetalis, and preterm delivery [91]. Untreated, the donor twin has an intrauterine death rate of 35–55%, and those that do survive are born on average at 29 weeks' gestation [92, 93]. Effective fetal treatment of TRAP involves abolishing the vascular anastomoses between the twins, which leads to the death of the nonviable fetus.

The most successful therapeutic option for treatment of TRAP is either laser or radiofrequency ablation at the base of the nonviable twin's umbilical cord [94]. After ablation, the survival rate of the remaining fetus increases to 80%, with an average delivery at 37 weeks [95]. Complications after treatment of TRAP include preterm rupture of the membranes, preterm delivery, and fetal demise. Anesthetic management for these procedures typically involves maternal local anesthesia with minimal sedation [70].

Twin-to-Twin Transfusion Syndrome (TTTS)

TTTS is a pathologic condition seen in monochorionic twins when a significant number of arteriovenous anastomoses exist between the two fetuses [96, 97]. Unequal sharing of placental blood flow between the twins results in discordant growth. Although some degree of shared arteriovenous blood flow exists in 90% to 95% of all monochorionic twins, normally these anastomoses are insignificant and partially balanced by protective arterioarterial connections, which equalize the resistance and blood flow [98, 99] (Fig. 14.3).

With unbalanced flow, TTTS results in increased blood delivery to one twin (the "recipient"), who experiences polyhydramnios, polycythemia, and polyuria, with severe cases leading to fetal cardiomyopathy and hydrops fetalis. The decreased flow to the other twin (the "donor") results in oligohydramnios and growth restriction, with severe cases leading to renal failure, heart failure, and hydrops fetalis [96]. Diagnostic criteria require the presence of a monochorionic diamniotic twin pregnancy and a discrepancy of amniotic fluid volume, with one twin having a maximal vertical pocket of greater than 8 centimeters and with the other twin having a maximum vertical pocket of less than 2 centimeters [100]. The Quintero staging system is the most commonly used metric to quantify the severity of the disease, which when combined with fetal echocardiography is of important prognostic value [101–103].

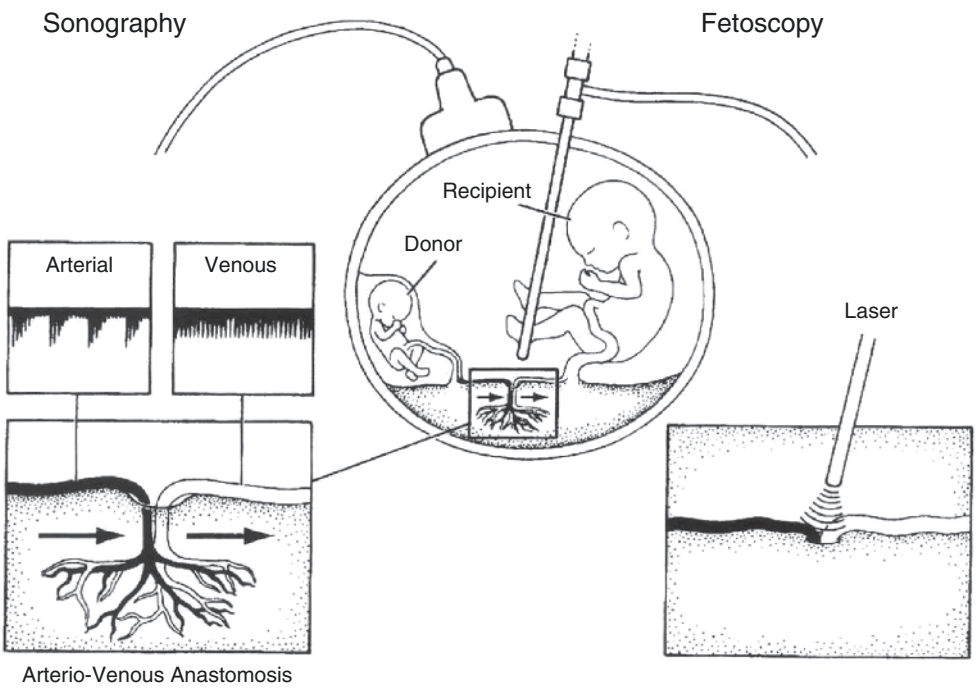

Fig. 14.3 SFLP for TTTS. Selective fetoscopic laser photocoagulation is used to treat monochorionic twin receiving unequal placental blood flow, resulting in TTTS. A fetoscope is placed into the amniotic cavity under ultrasound guidance. A laser is used to ablate arteriovenous anastomoses between the twins, resulting in more equal placental blood flow. From Graves CE, Harrison MR, Padilla BE.Minimally Invasive Fetal Surgery. Clin Perinatol. 2017 Dec;44(4):729–751. With permission from Publisher

Previous therapeutic efforts centered on amnioreduction of the polyhydramniotic twin; however, survival of both fetuses is only about 60% with this technique [104, 105]. A more recent approach involves selective fetoscopic laser photocoagulation (SFLP), whereby abnormal arteriovenous connections are identified by ultrasound and selectively ablated in stage II–IV twins between 18 and 26 weeks' gestation [106]. A 2004 randomized, multicenter trial demonstrated improved overall survival and neurologic outcome for patients treated with SFLP compared with amnioreduction [107]. Unfortunately, neurologic injury remains a concern, even in treated fetuses, with major neurological sequelae, such as cognitive impairment, motor delay, and cerebral palsy that affects 3–25% of treated twins [108]. Additionally, preterm premature rupture of membranes occurs in up to 30% of SFLP-treated pregnancies [96, 106]. Anesthetic technique for SFLP in TTTS typically involves maternal local anesthesia with or without sedation [70]. Alternatively, neuraxial anesthesia can be employed.

Congenital Heart Disease

Though congenital heart defects are common fetal anomalies, few are amenable to fetal intervention. Treatment of these lesions attempts to halt or reverse the effect of the defect before permanent damage can occur. Present fetal cardiac therapies include (1) aortic balloon valvuloplasty for treatment of critical aortic stenosis and evolving hypoplastic left heart syndrome (HLHS); (2) atrial septostomy in HLHS with an intact or very restrictive atrial septum; (3) pulmonic balloon valvuloplasty for pulmonary atresia or hypoplastic right heart with an intact ventricular septum; and (4) pericardiocentesis for congenital cardiac tumors or aneurysms [109, 110].

Of these fetal procedures, the most commonly performed is aortic valvuloplasty for evolving HLHS. This intervention can improve neonatal stability and allow for a biventricular postnatal outcome [111–113]. In this procedure (Fig. 14.4), ultrasound is used to guide a cannula through the maternal abdomen, into the uterus, through the fetal chest wall, and into the left ventricular outflow tract, where a balloon is deployed at the level of the aortic valve [114]. Maternal neuraxial anesthesia is most typically chosen for this procedure, although general anesthesia is occasionally used to allow for uterine relaxation for improved fetal positioning. Fetal immobility is ensured by administering a fetal intramuscular injection of muscle relaxant with fentanyl, and fetal resuscitation drugs for intramuscular or intracardiac injection must be readily available [115]. Fetal complications include bradycardia, pericardial effusion, ventricular thrombosis, preterm delivery, and fetal death, with technical success present in 75% of cases [112, 116].

Obstructive Uropathy

Lower urinary tract obstruction (LUTO) in the fetus can occur at the level of the ureteropelvic junction, the ureterovesical junction, or the urethra. A high perinatal mortality rate (90%) occurs when the obstruction is bilateral or urethral; survivors usually exhibit significant renal impairment [117, 118]. LUTO is diagnosed after oligohydramnios is

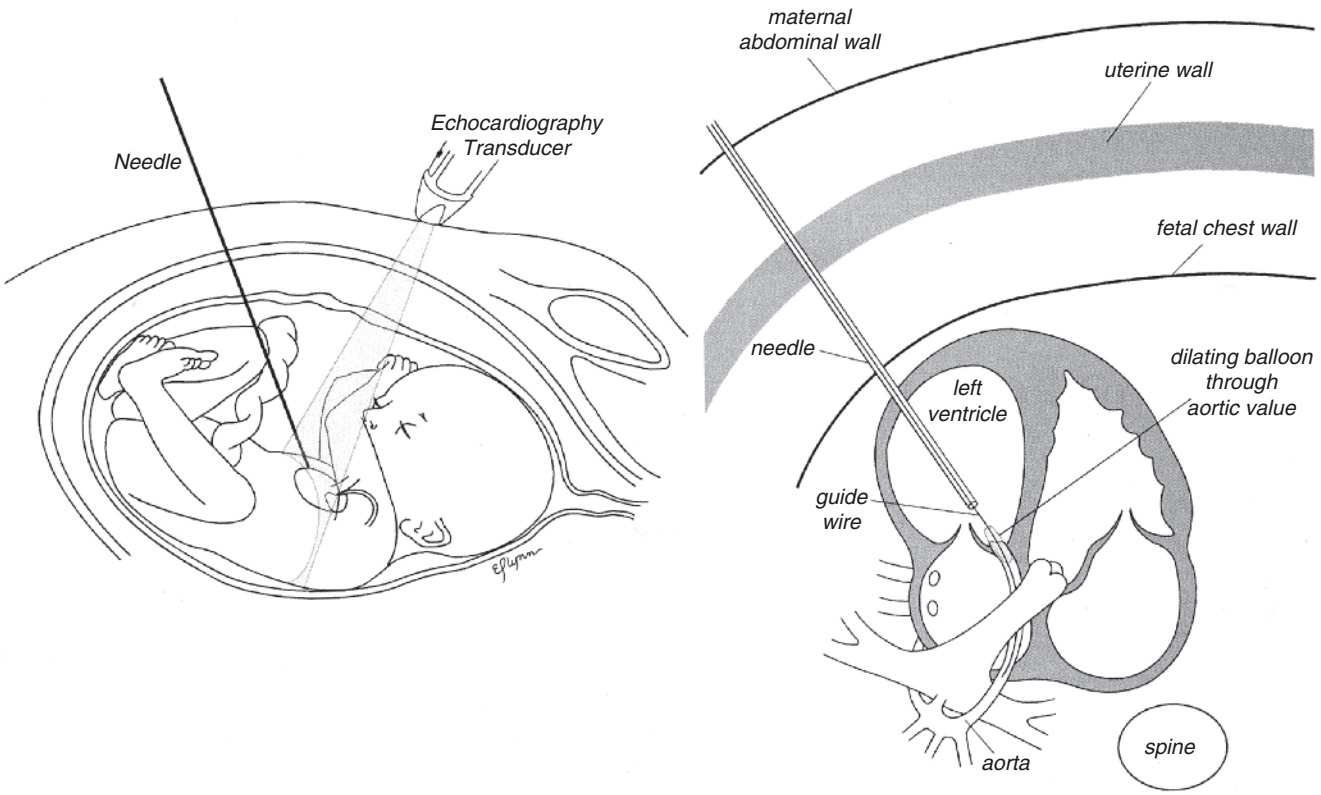

Fig. 14.4 Percutaneous fetal aortic balloon valvuloplasty. Percutaneous fetal aortic balloon valvuloplasty is used in cases of evolving HLHS. Ultrasound guidance is used to direct a balloon-tipped cannula introducer through the maternal abdomen and uterus and into the apex of the fetal heart. The tip of the cannula is positioned in the left ventricular outflow tract; the balloon is guided into the aortic valve and inflated. From reference 113 with permission

noted on antenatal ultrasound; the oligohydramnios results from inadequate urine production [119]. LUTO is classified by amniotic fluid index, renal imaging, and fetal urine chemistry. Morbidity correlates with the timing of onset, gender, severity of obstruction, concentration of urine electrolytes, and location of the obstruction [120–122].

Vesicoamniotic shunting involves placing a double-coiled, valveless stent between the fetal bladder and the amniotic cavity, usually under local anesthesia with ultrasound guidance. Shunt placement improves bladder development, increases amniotic fluid volume, and assists with lung development [123]. Procedural complications include fetal trauma, gastroschisis, preterm premature rupture of the membranes, preterm delivery, and infection [124]. A reduction in mortality has been reported after placing a fetal shunt, compared with standard of care, although long-term morbidity and renal function are similar among treated and untreated survivors [125–128].

An alternative strategy to vesicoamniotic shunting involves fetal cystoscopy. Fetal cystoscopy can be used to determine if LUTO results from urethral atresia or posterior urethral valves. Ablation of posterior urethral valves with cystoscopy may improve renal function when compared with shunt placement [129].

Congenital Diaphragmatic Hernia (CDH)

CDH is a condition where fetal abdominal contents herniate through a defect in the diaphragm into the thoracic cavity. Neonates suffer from pulmonary hypoplasia, pulmonary hypertension, and respiratory insufficiency. The prognosis of infants with a CDH is often quantified based on the ratio of fetal lung area to head circumference (LHR) as well as the presence of liver herniation into the thoracic cavity. With postnatal repair, infants with an LHR < 0.7 and liver herniation do not survive, whereas an LHR > 1.4 is associated with a 73% survival rate [130]. Because LHR varies with gestational age, an observed-to-expected LHR (O/E LHR) can be used to account for this difference [131, 132]. The MRI measurement of the fetal observed-to-expected total lung volume is another method of antenatal assessment for prognosis [133, 134].

Initial attempts at fetal CHD repair were open procedures and did not improve the postnatal outomes [135]. More recently, the focus has shifted to mechanically occluding the trachea to prevent the egress of fetal lung fluid and therefore increase pulmonary hydrostatic pressure and promote lung maturation. After a series of refinements, this technique involves placing a balloon into the fetal trachea using fetos-

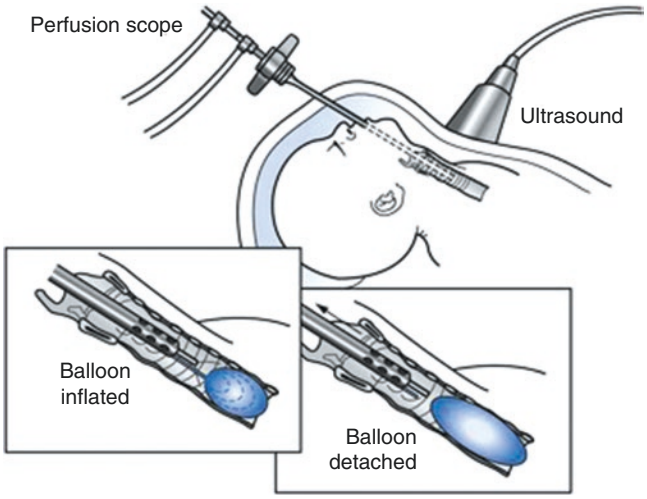

Fig. 14.5 Fetal tracheal balloon occlusion for CDH. Tracheal balloon occlusion is a technique used in fetuses with CDH. The goal of occluding the trachea of fetuses with CDH is to increase lung volume, decrease herniation of abdominal viscera, and improve postnatal lung function. The procedure involves a single intrauterine trocar, through which a fetoscope is introduced into the fetal trachea. A balloon is inflated just proximal to the carina. The balloon is usually removed at 34 weeks' gestation with a second fetal procedure. Reproduced with permission from Harrison MR, Albanese CT, Hawgood SB, et al. Fetoscopic temporary tracheal occlusion by means of detachable balloon for congenital diaphragmatic hernia. Am J Obstet Gynecol 2001; 185:730–3

copy (Fig. 14.5) [136]. Initially, balloons were left in place until delivery, which required an EXIT procedure (detailed later), but now tracheal balloons are typically removed with a second fetoscopic procedure, usually near 34 weeks' gestation [137]. Maternal anesthesia for these procedures involves neuraxial anesthesia or local anesthesia at the trocar insertion site. Fetal anesthesia and immobility is typically achieved with an intramuscular fetal injection of muscle relaxant and fentanyl.

A 2016 meta-analysis reported that survival in fetuses with an LHR ≤ 1.0 who underwent fetal tracheal occlusion improved compared with a contemporary postnatal care control group [138]. Presently, an ongoing multicenter, prospective, randomized trial is comparing the outcomes after placing fetal tracheal balloon at both 27–30 weeks and 30–32 weeks and removing them at 34 weeks to standard postnatal management [139]. Long-term outcome data of the respiratory and neurological complications of endoscopic tracheal occlusion in the fetus are needed to better guide fetal therapy for the treatment of CDH.

Congenital Pulmonary Lesions

Congenital pulmonary airway malformations (CPAM) consist of five subtypes of cystic and/or solid benign pulmonary tumors [140, 141]. Though small lesions often regress, large or fast-growing lesions can lead to pulmonary hypoplasia, heart failure, and hydrops fetalis [142]. A ratio of lung tumor volume to head circumference (CVR) is used to predict hydrops fetalis and adverse postnatal outcomes, with a ratio of <0.56 unlikely to have adverse postnatal outcome and a ratio > 0.56 with a 33% positive predictive value for a poor outcome [143, 144]. A ratio of >1.6 is a marker of severe morbidity and can be used as an indication for fetal intervention [145]. Betamethasone can be administered to mothers with a high-risk fetal CPAM to improve fetal survival [146, 147].

Large macrocystic lesions or large pleural effusions leading to hydrops fetalis are managed by placing shunt catheters between the lesion and the amniotic cavity. Placing a thoracoamniotic shunt can improve hydrops fetalis, and lung lesions are subsequently resected after birth [148]. The shunt is usually placed using local or neuraxial anesthesia for the mother with intramuscular administration of muscle relaxant and fentanyl to the fetus. Shunts can malfunction, move, and cause bleeding, infection, or premature rupture of the membranes [140].

Some solid or mixed lesions cannot be shunted and may require open fetal resection. Open resection poses significant risks for the fetus, including hemorrhage and cardiovascular instability, which may require resuscitation of the fetus in utero [149]. Alternatively, in term or near-term fetuses, an EXIT procedure (see below) can be performed to facilitate tumor resection in the case of severe thoracic compression [150, 151].

SCT

SCT are usually diagnosed in the second trimester of pregnancy and may grow rapidly. In general, the tumors themselves are benign, although the cardiovascular side effects that result from the large arteriovenous shunt may cause high cardiac output heart failure, which in turn may lead to polyhydramnios and hydrops fetalis [152, 153]. The tumors can also rupture, precipitating preterm delivery or urinary tract obstruction. Tumors are staged by the Altman criteria [154], and fetal MRI can be useful for prenatal evaluation. Poor fetal outcome is associated with a tumor volume-to-fetal weight ratio > 0.1 cm^3/g before 24 weeks' gestation [155].

Antenatal treatment of SCT is reserved for fetuses with external tumors that are rapidly growing or diagnosed early in gestation early (<30 weeks) [156]. Both minimally invasive therapies and open fetal resection have been performed with unclear benefits between different techniques [153, 157]. Minimally invasive intervention involves radiofrequency ablation, embolization, or thermocoagulation of the vascular supply to the tumor and/or cyst draining. A review of minimally invasive interventions in 34 patients over 33 years revealed an overall survival rate of 44% in fetuses without preexisting hydrops and 30% in patients with

hydrops [153]. Open resection has been sucessuful [158] but remains relatively rare. Open fetal resection, like postnatal surgery, carries a high potential for blood loss. An intraoperative intravenous line is essential to resuscitate the fetus with volume. In rare cases, maternal mirror syndrome can develop in the case of fetal hydrops [159]. Mirror syndrome is similar to elements of preeclampsia in that the mother develops hypertension and peripheral and pulmonary edema. The development of mirror syndrome is quite serious and should lead to delivery, as it does not always resolve with fetal correction [159, 160].

MMC

MMC is due to incomplete closure of the neural tube, resulting in herniation of meninges and neural tissue through a vertebral defect. MMC causes lifelong defects, including loss of motor and sensory function below the level of the lesion, hydrocephalus, absence of bowel and bladder control, and cognitive impairment [161, 162]. The deficits associated with MMC are likely due to two subsequent processes: first the abnormal neural tube formation and, second, the compression of the neural tissues and their exposure to amniotic fluid. By closing the defect in utero, the secondary causes of damage are reduced, improving neurologic outcome (Fig. 14.6). This latter benefit was first demonstrated in a randomized trial of 183 patients in 2011 in which prenatal closure of MMC via open hysterotomy at 19–26 weeks was compared with the standard postnatal closure. Fetal repair reduced the need for placing a ventriculoperitoneal shunt, decreased hindbrain herniation, and improved motor function at age 30 months. Complications from the fetal repair included an increased risk of preterm delivery, respiratory distress syndrome, uterine dehiscence, and premature rupture of the membranes [163]. Analysis of long-term outcome data is ongoing, but the present evidence has demonstrated improved motor and behavioral outcomes for those patients who underwent prenatal repair [164–166]. Results of this trial are limited by strict inclusion criteria and performance of the procedures at one of three established fetal surgical centers [167, 168].

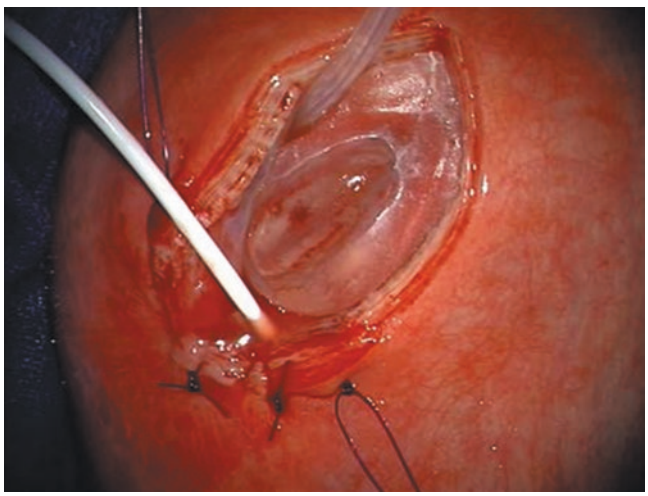

Fig. 14.6 Fetal MMC. Photograph depicts a uterine hysterotomy and fetus with a lumbar MMC undergoing open in utero fetal repair

More recently, the suitability of fetoscopic MMC repair to reduce the risk of a maternal hysterotomy and subsequent need for cesarean delivery has begun [169]. A 2017 meta-analysis of initial data suggested that a minimally invasive approach for MMC repair yielded a greater rate of preterm delivery, premature rupture of the membranes, and cerebral spinal fluid leakage but a reduced rate of preterm birth and uterine dehiscence [170]. Long-term outcome data are not yet available to compare for these two techniques.

Regardless of surgical technique, fetal repair of MMC requires meticulous anesthetic planning. Similar to open procedures, fetal repair requires profound uterine relaxation, fetal analgesia, and muscle relaxation, intraoperative fetal monitoring, and a plan for maternal postoperative pain management and maternal and fetal monitoring [54] (see "Management of Open Fetal Procedures," previously).

The Ex Utero Intrapartum Treatment (EXIT) Procedure

The EXIT procedure allows for partial delivery of the fetus while placental circulation is maintained to ensure adequate oxygenation and perfusion. Although initially developed for the removal of tracheal occlusive devices placed for in utero CDH treatment, the EXIT procedure is now used for a multitude of fetal anomalies including congenital airway lesions, intrathoracic masses, SCT resection, separation of conjoined twins, and as a bridge to extracorporeal membrane oxygenation [171, 172] (Table 14.4). The EXIT procedure requires a profound state of uterine relaxation to prevent placental separation from the uterus and maintain fetal-placental perfusion. EXIT procedures are most often performed under deep general anesthesia (>2 MAC), similar to open fetal procedures.

The anesthetic approach for preoperative evaluation and initial intraoperative management is similar to the approach previously described for open fetal surgery. A detailed meeting with all members from the multidisciplinary EXIT team should be arranged before the start of the case to ensure a uniform well-coordinated approach and availability of all necessary equipment and supplies. Cross-matched blood is obtained for the mother, and if a fetal surgical procedure is anticipated, compatible blood should also be available for the fetus. Weight-based fetal medications including epinephrine

Table 14.4 EXIT procedure indications

Procedure	Indications
EXIT to airway	Any anatomical cause of anticipated airway obstruction, including but not limited to: • Congenital high airway obstruction syndrome. • Laryngeal atresia/stenosis. • Tracheal atresia/stenosis. • Laryngeal web/cyst. • Cervical teratoma. • Cystic hygroma. • Hemangioma. • Lymphangioma. • Removal of tracheal occlusive device placed to treat CDH. • Severe micrognathia/retrognathia.
EXIT to resection	Resection of lesion causing mediastinal or airway compromise, including but not limited to: • Bronchogenic cysts. • Bronchopulmonary sequestration. • CPAM. • Mediastinal mass. • Thoracic tumor.
EXIT to ECMO	Anticipation of severe cardiopulmonary compromise necessitating extracorporeal circulatory support, including but not limited to: • CDH with severe pulmonary compromise. • Aortic stenosis with intact/restrictive atrial septum.
EXIT to separation	Separation of conjoined twins

(10 mcg/kg), atropine (20 mcg/kg), an opioid (fentanyl 10 mcg/kg), and muscle relaxant (rocuronium 2.5 mg/kg) should be prepared and passed onto the surgical field. In addition to direct fetal cardiac monitoring, a sterile fetal pulse oximeter is helpful to monitor the fetus and assist to confirm that the airway of the fetus was successfully intubated. A sterile ventilation source with a pressure manometer for the fetus, as well as sterile laryngoscopes, tracheal tubes, and intravenous supplies, is also prepared on the sterile field.

A preoperative epidural catheter should be placed for postoperative pain control in the mother. Large-bore intravenous access should be established for the mother as blood loss can be sudden due to profound uterine relaxation. Though an arterial line is not mandated, invasive monitoring should be readily available and initiated in the setting of any hemodynamic instability. General anesthesia is induced with a rapid sequence intubation. The concentration of inhalational anesthetic should be increased to ≥2 MAC to ensure adequate uterine relaxation, with prophylactic use of phenylephrine to maintain the mother's blood pressure within 10% of baseline for adequate placental perfusion. The maternal heart rate should be maintained near baseline values using anticholinergic agents to maintain cardiac output [22]. When general anesthesia is contraindicated, neuraxial anesthesia can be combined with a high-dose infusion of nitroglycerine (1–10 mcg/kg/min) to relax the uterus as well as an infusion of phenylephrine to support the blood pressure [79, 173, 174]. Although nitroglycerine can cross the placenta, the majority is metabolized at the placental interface resulting in minimal effects on the fetus [79, 173]. However, the optimal anesthetic technique for the EXIT procedure has not as yet been determined.

Once the uterus is exposed, a small hysterotomy is performed and extended with a stapling device. A pulse oximeter is then placed on the hand of the fetus and shielded from ambient light. The normal range for the oxygen saturation in the fetus is between 40% and 65%, before ventilation [175]. Warmed crystalloid fluids are instilled continuously into the uterine cavity to optimize the position of the fetus and to minimize pressure on the umbilical cord and placenta.

Depending on the indication, the duration of the EXIT procedure can last from a few minutes (i.e., tracheal intubation) to hours (i.e., resection of a large mass); anesthetic techniques have provided stability for long procedures [176]. Once the airway in the fetus has been secured (intubated) and ventilation is established, the oxyhemoglobin saturation should increase to ≥90%. Failure to increase fetal oxygen saturation represents an indication for transitioning the fetus to ECMO before clamping the umbilical cord and delivering the fetus. An end-tidal CO_2 monitor is also helpful to confirm the correct placement of the tracheal tube in the fetus.

After delivery, the anesthetic concentrations are decreased to promote uterine contraction and hemostasis. The inhalational anesthetic is discontinued or significantly decreased, and the nitroglycerine infusion is stopped, while other anesthetic agents such as propofol, remifentanil, and/or nitrous oxide are introduced to maintain adequate anesthesia and uterine tone [177, 178]. Oxytocin is administered, and other uterotonic medications such as Methergine and Hemabate may be administered as necessary to increase uterine tone. The trachea of the mother is extubated when she has fully regained consciousness.

Conclusions

Fetal treatment is an innovative and maturing field with a growing number of centers worldwide. The transfer of outcomes from existing data generated from a very specific patient population at a small number of academic centers to a larger population is unclear. Caution should be exercised when deviating from strict inclusion criteria or when minimal experience with a procedure exists. The multidisciplinary nature of fetal treatment requires cooperation and collaboration across disciplines. Ethical, social, and legal issues, such as maternal autonomy, and options for pregnancy termination further complicate the practice of fetal interventions [179, 180]. A bioethics committee, spearheaded by the American College of Obstetricians and Gynecologists and the American

Academy of Pediatrics, has established recommendations for fetal therapy for institutions [7].

Further research is needed to refine surgical techniques, to optimize surgical timing, and to define neonatal outcomes more clearly. Additionally, best anesthetic practices for these complicated cases have not been established and are presently based on animal models and retrospective, observational trials. Open, collaborative research networks are essential to advance this field.

Future directions in fetal treatment include the use of in utero stem cell and gene therapy [181], as well as the development of artificial placental units that utilize extracorporeal support to sustain the preterm neonate after delivery [182]. Fetal surgery is unique among modern-day surgery in that the lives of two patients, the mother and the fetus, undergo procedures concurrently. The anesthesiologist must support and consider both patients when participating in these complex cases.

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Neonatal Pain: Significance, Assessment, and Management

15

Joy M. Dawes and Richard F. Howard

Neonatal Pain Mechanisms

Nociceptors and sensory pathways are present from embryonic stages of development, although they undergo substantial postnatal reorganization and functional change. Sensorimotor coordination is refined and complex integrative central processing functions develop, particularly in the brain, through infancy, childhood, and adolescence, although some of the most important, rapid, and profound changes occur during the neonatal period.

Plasticity of the CNS or the capacity of the CNS to change and adapt is probably maximized during the neonatal period. In fact, such plasticity is essential for neural development, and "normal" levels of activity in nociceptive pathways are a mechanism by which this process is controlled.

The neonate is much more sensitive to nociceptive pain, i.e., noxious actual or potential tissue-damaging sensory inputs, than older children and adults. Stimulus-specific nociceptive thresholds are reduced at birth and increase gradually as a function of developmental age throughout infancy and childhood [1]. Modality-specific studies of thresholds to mechanical stimuli (touch, pressure) in infants from preterm to 3 months of age show a clear linear relationship between the mechanical force needed to trigger a reflex withdrawal response and chronological age [1, 2].

The response thresholds to touch, heat, and pain are reduced in neonates but gradually increase as the nervous system matures. These changes are mediated by alterations in the number, structure, and function of nociceptors, central neural connections, and the balance of activity in modulatory pathways; some of the most important are summarized in Table 15.1.

Painful mechanical, thermal, and chemical stimuli in adults are normally detected by high-threshold polymodal slow-conducting C and fast A-delta fiber nociceptors whose cell bodies are located in the dorsal root ganglion (DRG) and whose central terminals are mostly found in nociceptive-specific areas of the superficial dorsal horn of the spinal cord (laminae I and II, Fig. 15.1a). A-delta fibers terminate directly on ascending "projection" neurons in lamina I,

Table 15.1 Factors that augment the pain responses in the neonate compared with the adult

	Factor	Effect
1	Low-threshold A-fiber mechanoreceptors terminate centrally on nociceptive-specific relay pathways at birth	Weaker stimuli can activate pain-specific pathways
2	Relatively larger and more overlapping cutaneous receptive fields	Amplification of stimulus effect due to increased numbers of neurons activated
3	Poorly localized and diffuse sensorimotor connections in the CNS	Less anatomically specific and more generalized motor responses
4	Weak intrinsic inhibitory mechanisms in the spinal cord[a]	Relative augmentation of pain signal
5	Intracortical circuits and arousal systems poorly developed at birth	Operation of immature sensorimotor cortex is mainly reflexologic
6	Reduced descending inhibition[a]	Relative augmentation of pain signal
7	Combination of factors 1–6	Nociception and reflex withdrawal are activated at lower stimulus intensity as a function of lower developmental age

[a] Contributes to larger receptive field size

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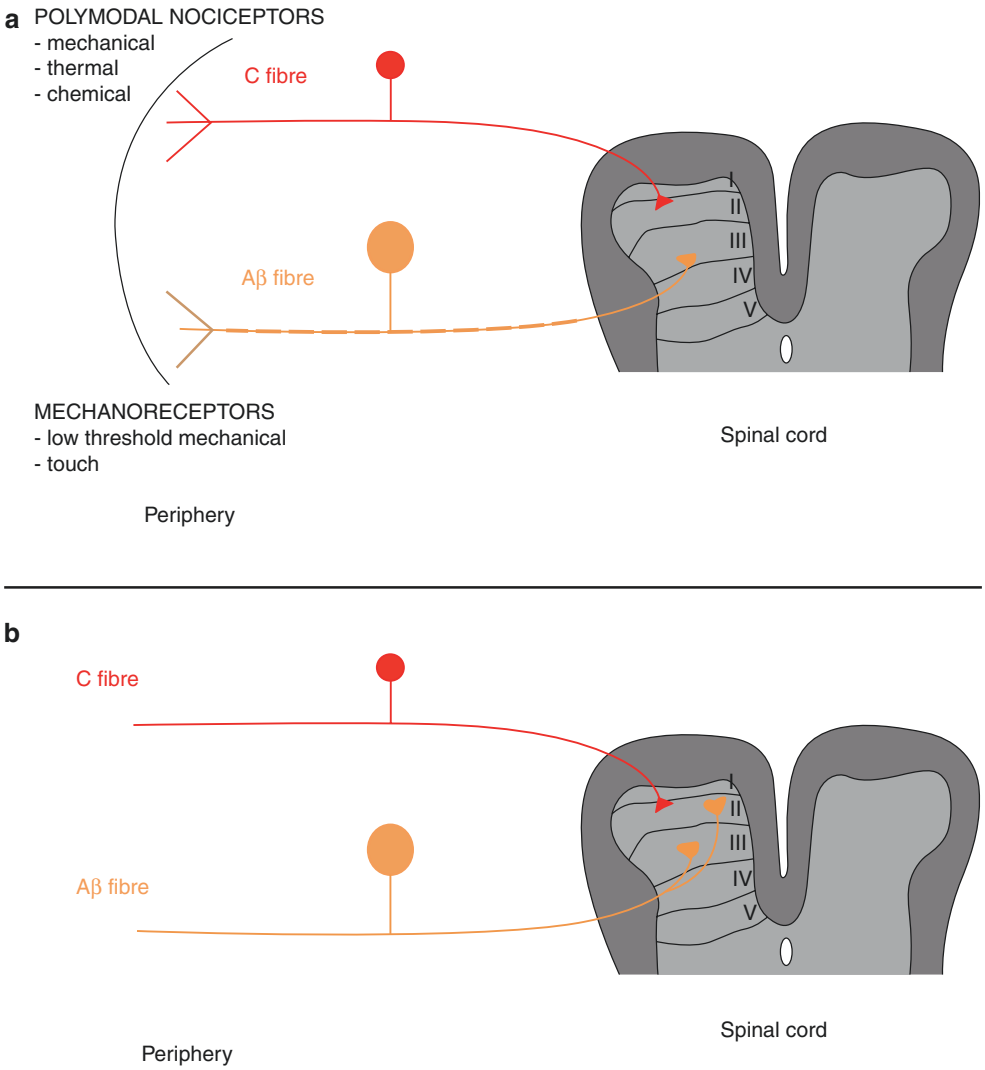

Fig. 15.1 (**a**) Adult sensory inputs. (**b**) Neonatal sensory inputs

whereas C fibers generally terminate on interneurons located in lamina II. Fast-conducting A-beta fibers mostly detecting innocuous touch and pressure normally terminate in deeper laminae of the cord.

However, in early development, the central terminals of A-beta fibers temporarily overlap with C-fiber terminals in pain-specific areas of lamina ll [3], withdrawing later to deeper laminae (Fig. 15.1b), thereby potentially activating nociceptive projection neurons when activated by low-threshold stimuli. In addition, as spinal nociceptive withdrawal reflex pathways are also activated, the threshold for evoking a reflex response is also reduced [4]. A reduction in specificity due to this structural difference is augmented by lack of myelination and immature ion channel kinetics that alter neuronal conduction times and synaptic strength leading to a more diffuse central response to peripheral stimuli. Within the spinal cord, there is a relative excess of excitation and delayed development of both local and descending inhibitions [3, 5–7], which contribute to these low-threshold and generalized reflex responses. In the neonate, strong tactile A-fiber input facilitates activity-dependent synaptic strengthening in the dorsal horn, but this declines with strengthening of nociceptive C-fiber input, which drives the maturation of targeted glycinergic inhibition [6]. This lack of specificity, organization, and control is mirrored in motor circuits such that output responses are also more diffuse and less well integrated spatially and temporally [8]. Physiological studies have confirmed that painful inputs in preterm infants transmit measurable responses from at least 24 weeks postconception [9]. The developing sensorimotor cortex expresses intermittent activity bursts that are organized as oscillations to support synchronization and plasticity in developing circuits [10]. Activity in the immature sensorimotor complex is predominantly driven by thalamic input provided by sensory feedback from spontaneous movement and passive tactile stimulation [10]. Tactile input plays an important role in activity-dependent maturation of the CNS. Evidence that afferent nociceptive signals reach the somatosensory cortex in preterm and term neonates has been demonstrated using near-infrared spectrometry (NIRS) [11, 12] and electroen-

cephalogram (EEG) recordings [9], which shown alterations in cortical activity after heel lance for blood sampling [13]. Specific postnatal functional stages in maturation of the nociception cortex have been demonstrated using electrocorticogram (ECoG) recordings in rat pups between 2 and 4 weeks of age [14]. Heel lance also produces spatially widespread nociceptive event-related potential (nERP) responses in the majority of neonates, and interestingly this widespread pattern is more likely to occur in females indicating the presence of pain-related gender differences from birth [15].

Using fMRI, the network of brain regions that are active after acute noxious stimulation in neonates has been identified and the activity compared with that observed in adults. Significant infant brain activity was observed in 18 of the 20 active adult brain regions but not in the infant amygdala or orbitofrontal cortex. Brain regions that encode sensory and affective components of pain were active in infants and showed variations with stimulus modality and intensity [16], suggesting that the infant pain experience resembles that observed in adults [17]. Resting state networks of synchronously active brain regions (including sensorimotor, default-mode, and salience networks) can be identified in term neonates suggesting that functional connectivity is already operational at this time [18, 19]. Secondary hyperalgesia appears to be less prominent at younger ages and is slower to develop [20]. Nonetheless, persistent alterations in nociceptive processing can occur after tissue injury in the neonate, leading to an exacerbated degree of hyperalgesia after a subsequent insult to the same somatotopic region [21].

Many aspects of maturation are subject to activity-dependent developmental control, and it has therefore been a concern that "abnormal" events such as severe pain in the neonate may alter normal development and lead to adverse long-term consequences to sensory processing mechanisms. In fact, surgery or injury during the neonatal period has been associated with changes in nociceptive thresholds and the response to subsequent painful stimuli, months or even years later, although the precise mechanisms involved and the exact roles of pain intensity and analgesia are still not fully understood [8, 22, 23]. Neonatal surgical injury in an animal model alters the postnatal development of RVM descending control, resulting in a predominance of descending inhibition and generalized reduction in baseline reflex sensitivity. This response was prevented by effective local anesthetic blockade highlighting the importance of neonatal perioperative analgesia [24].

Significance of Neonatal Pain

The increased sensitivity of neonates to nociceptive inputs is important. Studies measuring the "stress" response to major surgery in neonates who received a "light" general anesthetic have demonstrated a massive, robust, and potentially harmful neuroendocrine stress response to pain, which was prevented by deeper levels of anesthesia and analgesia, even at the youngest ages [25, 26]. In addition, pain relief during and after surgery improved immediate postoperative physiological outcomes such as respiratory function in infants after major surgery [26]. As surgery in the neonatal period has been associated with changes in pain perception of greater duration, at least some of which can be prevented by analgesia, it may be that unmodified and abnormally increased levels of activity such as during surgery without anesthesia or severe pain without analgesia contribute, in part, to these changes. For example, boys who underwent neonatal circumcision without analgesia showed an enhanced response to pain 3 months later during immunization compared with those who received analgesia during their circumcision or were not circumcised [27]. Infants who had abdominal surgery repeated in the same dermatome as a previous operation before 3 months of age exhibited increased pain responses and analgesic requirements compared with controls [22]. Even "minor" procedures such as heel lance blood sampling can cause significant pain in the neonate [28]. They too can lead to augmentation of the response to subsequent pain or may even be associated with more serious morbidity and poorer outcomes especially when repeated frequently, e.g., in NICU [29].

Complex and subtle effects have occurred in cohorts of ex-preterm children who had surgery as neonates and spent time in the NICU. A relative increase in temperature and touch thresholds near the site of surgery has been observed, but some children also have a more generalized decrease in temperature threshold [23, 30, 31]. Persistent sensory loss and/or gain (punctate and dynamic mechanical allodynia) have been demonstrated next to scars many years after neonatal surgery [32]. Changes in somatosensory function in adolescents after neonatal intensive care vary depending on the initial exposure (e.g., gestational age at birth, requirement for surgery, duration of intensive care), type and intensity of experimental stimulus, and age at follow-up [33].

The degree to which persistent changes in somatosensory function correlate with altered response to future injury has been demonstrated in animal studies but requires further evaluation [34]. In the laboratory, repeated touch and needle prick stimulation in the neonatal period can alter adult spinal sensory neuronal sensitivity to both innocuous and noxious mechanical stimulations [35]. Effects of tissue injury include altered ion channel expression in primary afferent and spinal cord neurons, shifts in the balance between synaptic excitation and inhibition within the superficial dorsal horn network (SDH), and priming of microglial responses in the adult SDH [21].

Adults who have experienced neonatal injury display increased pain and injury-induced hyperalgesia in the affected

region. Proposed mechanisms for this include peripheral nerve sprouting and dorsal horn central sensitization, disinhibition, and neuroimmune priming. However, mild injury can also induce widespread baseline hyposensitivity across the rest of the body surface which may be a result of altered descending pain control systems driven, in part, by changes in the stress/hypothalamus-pituitary axis (HPA) [36].

In the laboratory, maturation of nociceptive reflexes can be delayed or abolished by blocking sensory inputs with local anesthesia (LA) for long periods [37]. NMDA receptor activity is important for normal sensory development in rat pups as chronic NMDA receptor blockade prevents the normal withdrawal of A-fibers from lamina II described above and a consequent persistence of low sensory thresholds [38].

Effects of Analgesics

The pharmacodynamic profile of analgesic interventions may not only be affected by age but also sex and type of intercurrent injury [39, 40]. A number of drugs and chemical compounds may also cause long-term adverse effects when administered in the neonatal period over and above any altered pharmacokinetic or pharmacodynamic responses due to immaturity. Neuroapoptosis, or programmed cell death, is a component of normal maturation in which cells that do not form functional connections are eliminated. Drugs that are NMDA antagonists and/or GABA agonists, in particular, have the potential to markedly increase apoptosis to such an extent that neural development is damaged leading to measurable deficits in, e.g., memory and learning. Although these effects have only been demonstrated in animal models to date, many general anesthetic agents have been implicated including ketamine (see below), a potent nonspecific NMDA antagonist that is also used as an analgesic.

These important considerations will impact how we assess and manage neonatal pain such that considerable specialist knowledge and skills are needed in order to deliver safe, effective, and developmentally appropriate care.

Assessment of Neonatal Pain

Assessing pain frequently is essential in order to manage pain well, although this too can present problems in immature and preverbal infants. Accurately assessing pain, including pain intensity, prevents or identifies pain, as well as monitors the effectiveness of administered analgesia [41]. Overall, there are three fundamental approaches to assessing pain in children:

- Self-report: an individual's personal description of pain and rating of intensity.
- Behavioral: observation of changes in facial expression and body posture due to pain.
- Physiological: measurement of changes in physiological arousal consequent to pain.

Obviously, self-report is impossible in neonates, and therefore an indirect measure of pain must be used. This has disadvantages; perceived pain intensity depends on many subjective influences apart from the degree of injury and tissue damage. Stress, anxiety, attention, and expectation, which are modulated by context, mood, previous experience, and underlying personality traits, all contribute to the degree of unpleasantness of pain; given our present knowledge of neurodevelopment, the extent to which such factors can influence pain perception in the neonate is largely therefore a matter of speculation.

Nevertheless, in neonates, observing behaviors such as facial expression, cry, and posture together with measuring physiological variables such as heart rate and blood pressure have been used to assess pain and gauge its intensity in the absence of viable more objective alternatives. Physiology-based markers such as near-infrared spectroscopy (NIRS) [42, 43], heart rate variability (HRV) [44, 45], and skin conductance have been studied but are not yet fully validated [46].

However, these surrogate measurements and markers may not be indicative of pain to the same extent, and a statistical technique called the item response theory may provide useful information regarding the informativeness of a given item [46]. A recent study demonstrated that when two assessment scales were compared, the behavioral items corresponded most closely with pain, whereas the physiological items corresponded least closely [47]. These observations and measures are subject to many external and internal influences aside from pain, which also poses difficulties for interpretation. For physiological variables in particular, a reduction in their reliability tends to occur over time due to homeostatic controls. In an attempt to improve accuracy, observations and measurements have been frequently incorporated into multidimensional pain measurement "tools" or "instruments" that are generally presented as checklists or scoring systems; the range of such observations and their validity and usability have been reviewed recently [48–51].

An EEG-based measure of infant nociceptive brain activity that is evoked by acute noxious stimulation and is sensitive to analgesic modulation has recently been presented and validated [52]. This provides an objective outcome measure that can be used in clinical trials of analgesics [53].

Pain Measurement Tools

A bewilderingly large number of pain assessment tools or scales have been designed for use in the neonate, some

Table 15.2 Pain assessment tools

Validated pain assessment tools
BIIP [58] Behavioral Indicators of Infant Pain (BIIP) BPS [59] Behavioral pain score BPSN [60] Bernese Pain Scale for Neonates (BPSN)
CHIPPS [61] Children's and infant's postoperative pain scale
COMFORT [62–64] COMFORTneo [65] COVERS Neonatal pain scale [66]
CRIES [67] Crying Requires Increased oxygen administration, Increased vital signs, Expression, Sleeplessness
CSS [68] Clinical Scoring System
DSVNI [69] Distress scale for ventilated newborn infants DAN [70] Douleur Aigue du Nouveau-ne EDIN [71] Echelle Douleur Inconfort Nouveau-Ne FANS [72] Faceless Acute Neonatal Pain Scale (FANS) Leuven Neonatal Pain Score
LIDS [73] Liverpool infant distress scale
NFCS [74] Neonatal facial coding system
NIPS [75] Neonatal infant pain scale PAIN [76] Pain Assessment in Neonates
PAT [77, 78] Pain assessment tool
PIPP [79] Premature Infant Pain Profile PIPP-R [80, 81] Premature Infant Pain Profile-Revised
SUN [82] Scale for use in newborns N-PASS [83]

Table 15.3 The PIPP [79] pain assessment tool[a]

Gestational age	
> = 36 weeks	0
32 weeks to 35 weeks 6 days	1
28 weeks to 31 weeks 6 days	2
<28 weeks	3
Behavioral state	
Active/awake eyes open facial movements	0
Quiet/awake eyes open no facial movements	1
Active/sleep eyes closed facial movements	2
Quiet/sleep eyes closed no facial movements	3
Heart rate maximum	
0–4 beats per minute increase	0
5–14 beats per minute increase	1
15–24 beats per minute increase	2
> = 25 beats per minute increase	3
Oxygen saturation minimum	
0–2.4% decrease	0
2.5–4.9% decrease	1
5.0–7.4% decrease	2
7.5% decrease or more	3
Brow bulge	
None (< = 9% of time)	0
Minimum (10–39% of time)	1
Moderate (40–69% of time)	2
Maximum (> = 70% of time)	3
Eye squeeze	
None (< = 9% of time)	0
Minimum (10–39% of time)	1
Moderate (40–69% of time)	2
Maximum (> = 70% of time)	3
Nasolabial furrow	
None (< = 9% of time)	0
Minimum (10–39% of time)	1
Moderate (40–69% of time)	2
Maximum (> = 70% of time)	3
Score total (0–21)	

[a]A revised version PIPP-R is also available that has undergone initial validation and is available in translated formats [80, 81, 85]

examples of which are given in Table 15.2. There is a considerable research literature on the subject, and it is now agreed that in order to be "fit for purpose," a pain assessment tool should have undergone a rigorous process of development. To be considered reliable, an individual tool must be validated in the patient population, clinical context, and the type of pain (e.g., postoperative or procedural) for which it is to be used. Despite the proliferation and availability of tools, these processes have not always been completed adequately nor have they been used consistently or well including inconsistencies having been identified between reported assessment practice and documented practice [54–56]**.** A large prospective multicenter cohort study in 243 NICUs in 18 countries (EUROPAIN) found that assessments of continuous pain occurred in less than one-third of NICU admissions and daily in only 10% of neonates [57]. Several factors may be responsible for this situation. Limitations of individual scales mean that no single one can be universally recommended for use in all neonates in every situation, and "usability" factors that lead to individual user preferences which might not be scientifically appropriate.

Selecting an Appropriate Pain Assessment Tool

Recommendations and guidelines have been produced by a number of professional bodies outlining the presently available tools and advising on their suitability for different circumstances [48, 50, 51]. Training and support are required for successful implementation of the best-validated tools, and this should be combined with ongoing monitoring and audits of practice. Some of the most widely endorsed tools include the PIPP [79], CRIES [67], and COMFORT [62] scales. The PIPP (Table 15.3) creates a score from 18 to 21 depending on gestational age and behavioral state, with 0–6 reflecting no pain, 6–12 reflecting mild-moderate pain, and above 12 indicating severe pain; it is suitable for procedural pain and ongoing postoperative pain. PIPP has now been revised to enhance validity and feasibility, and initial construct validation of PIPP-R has been demonstrated [80, 81]. CRIES includes similar indicators to PIPP: crying, oxygen requirements, increases in heart rate or blood pressure, facial expression, and sleep behavior. CRIES yields a score ranging from 0 to 10, similar to most self-report or observational measures of pain. The COMFORT [63] tool is more complex than the other scales. Originally developed in 1992, COMFORT assessed global comfort in the pediatric inten-

sive care, having undergone several validation studies for both procedural and ongoing postoperative pain. It is frequently chosen for use in the sickest neonates, e.g., after cardiac surgery. The tool has now been modified for neonate (COMFORTneo) and showed preliminary reliability [65].

The EDIN scale and N-PASS tools were developed to assess more prolonged pain in the neonatal period; validity and reliability studies for both scores have been described [71, 83]. The scores used most frequently in the EUROPAIN study, a prospective cohort of practice in 243 NICUs in 18 European countries, included the EDIN scale (56.7%), COMFORTneo behavioral scale (19.7%), N-PASS (13.2%), and the COMFORT scale (10.1%) [84].

Management of Pain

Information and Protocols: Pain Management Plans

The provision of training and education for healthcare workers and availability of written and verbal information for families and caregivers are pivotal for successful pain management. Analgesic regimens should be pre-planned wherever possible and implemented with supporting educational programs, provision and maintenance of necessary equipment, and clear developmentally appropriate management protocols. Pain management protocols must be sufficiently flexible to allow for differences in analgesic requirements due to developmental age and other factors; they should include a pain assessment and reassessment plan, encompass management of background and incident (breakthrough) pain, and stipulate monitoring and management of adverse effects.

A well-designed protocol will therefore ensure efficacy and uniformity of treatment and facilitate ongoing evaluation of effectiveness. Protocols for pain management should also be designed in conjunction with ongoing global management strategies such as family-centered and developmental care [86]. The implementation of family-centered care involves establishing a partnership between parents or caregivers and nursing staff and other healthcare workers that substantially increases parents' role in their child's in-hospital care. Developmental care in NICU is a strategy for reducing stress-related morbidity in premature neonates; stressful and painful inputs are reduced by observing individual responses and carefully reorganizing and planning care [87].

Multimodal or Balanced Analgesia

Present strategies for the treatment of acute pain are centered on the concept of multimodal analgesia, which was first proposed in order to increase the efficacy of analgesics while reducing their adverse effects [88]. The supporting rationale is that the major pharmacological groups of analgesics act on different components of pain pathways and as such their effects are likely to be complementary. This is also likely to be true in the neonate, but developmental factors influencing the effects and therefore appropriateness of many analgesics must also be considered. It is logical to use combinations of analgesics, such as acetaminophen, opioids, and local anesthetics in conjunction in order to achieve the optimum effect while keeping the dose of each, and therefore side effects, at a moderate level. Sucrose and non-pharmacological pain management strategies such as nonnutritive sucking (NNS), swaddling, massage, etc., also have an important place in managing neonatal pain, particularly for procedural pain, and should therefore be included in a multimodal regimen where it is appropriate

Pharmacological Methods

Relatively few analgesics have a clearly established role for managing neonatal pain. For a detailed discussion of the clinical pharmacology of analgesics in neonates, readers are referred to Chap. 3

Acetaminophen (Paracetamol)

Acetaminophen is an effective antipyretic and analgesic that has been widely used for all ages, including premature neonates. Acetaminophen is commonly used to manage pain of mild to moderate severity, as more severe pain is incompletely managed by acetaminophen alone. It is often combined with more potent analgesics to manage postoperative pain. Acetaminophen can be administered orally, rectally, or intravenously. Although one study showed no additional effect when rectal acetaminophen was combined with morphine after major surgery in neonates [89], marked variations in plasma concentrations were noted. An RCT in neonates and infants showed a lower cumulative morphine dose over 48 h with intermittent intravenous acetaminophen compared with continuous morphine after major surgery [90].

The precise mechanism of action of acetaminophen is unknown, but central cyclooxygenase (COX) inhibition is probably important [91]; other mechanisms have also been proposed including NMDA and serotonin antagonism [92] and a possible action of the metabolite *N*-arachidonoylphenolamine (AM404) on the cannabinoid CB1 receptor [93]. Alterations in the pharmacokinetic handling of acetaminophen have significant implications for safe dosing in neonates. Gastrointestinal absorption is delayed in premature neonates, whereas rectal bioavailability is initially greater in the premature and then decreases toward the usual value of 0.5 with increasing age [94]. The volume of distribution decreases and clearance increases from 28 weeks postconceptional age, resulting in a gradual decrease in the elimination half-life.

Acetaminophen is predominantly metabolized by phase II enzymes to acetaminophen glucuronide and acetaminophen sulfate. The remainder is metabolized to the hepatotoxic metabolite NAPQI through the action of cytochrome P450 enzymes such as CYP2E1, CYP1A2, CYP3A4, and CYP2A6 [95]. Under usual circumstances, reduced glutathione neutralizes NAPQI very rapidly [46]. Glucuronidation of acetaminophen is poorly developed in premature infants and matures during early childhood, whereas sulfation remains fairly constant [96]. CYP enzymes also mature in infancy, but data on NAPQI formation in neonates is lacking [46]. There have been cases of accidental IV acetaminophen poisoning in neonates [97, 98], and concerns have been raised about the risk of accidental administration of mL rather than mg. However, there are few reports of hepatotoxicity after overdose, particularly when the antidote, *N*-acetylcysteine (NAC), is administered promptly [98].

Dose guidelines based on formulation, route of administration, weight, and developmental age have been determined by pooled population analysis (Tables 15.4 and 15.5). Weight has been shown to be the most important predictor of acetaminophen clearance in neonates [99, 100]. Clearance is reduced in premature neonates than in term neonates, although there is large interpatient variability [96].

Antipyretic plasma levels are 10–20 mg/L, levels required for analgesia are thought to be similar, and so most dosing regimens attempt to target the trough plasma concentrations at 10 mg/L [101]. A greater initial dose followed by maintenance doses that did not exceed the recommended maxima is generally recommended. Peak plasma levels are rapidly achieved after oral ingestion, although there is a 1–2 h lag before the maximum therapeutic effect. In contrast, the onset of analgesia after IV administration may be much faster [102], with a more predictable PK profile [103]. As rectal bioavailability is much poorer and more variable than oral dosing, larger initial doses are recommended when rectal acetaminophen is administered, except in the premature neonate.

Intravenous acetaminophen is not licensed for premature neonates in Europe nor for those less than 2 years old in the USA, and therefore a variety of dosing regimens are used off-label.

Comprehensive data analyses have now been undertaken for the use of IV acetaminophen in neonates, which take into account size, clearance maturation, effect, and safety [100, 104–106]. A population PK study of 158 neonates (27–45 weeks' PMA) recommended a loading dose of 20 mg/kg followed by a maintenance dose of 10 mg/kg every 6 h for neonates aged 32–44 weeks' PMA [100], which would achieve steady-state plasma concentrations associated with reasonable analgesia and is supported by short-term safety. For premature neonates <32 weeks, increasing the interval between repeat maintenance doses to 12 hourly has been recommended [107]. A more recently generated set of concentration time profiles for neonatal pain suggested a loading dose of 12 mg/kg and a maintenance dose of 6 mg/kg/6 h in <32 weeks' PMA neonates. This regimen was shown to lead to target C_{ss}mean of approximately 10 mg/L, although additional clinical studies are needed to support its safety [108]. For older infants and children, a dosing regimen of 15 mg/kg every 6 h is commonly used [107].

Nonsteroidal Anti-inflammatory Drugs (NSAIDs)

NSAIDS for analgesia are not presently used in neonates because uncertainty regarding their efficacy and potential for adverse effects results in an unfavorable benefit-risk ratio. Laboratory studies have shown a reduced efficacy of NSAIDS in young rodents casting doubt on their value as analgesics in infants [109].

NSAIDS act by inhibition of cyclooxygenase, enzymes that regulate many cellular functions by the production of prostaglandins and other substances. Prostaglandins have

Table 15.4 Acetaminophen dosing guide—oral and rectal administration

Age	Route	Loading dose	Maintenance dose	Interval	Maximum daily dose	Duration at maximum dose
28–32 weeks' PCA	Oral	20 mg/kg	10–15 mg/kg	8–12 h	30 mg/kg	48 h
	Rectal	20 mg/kg	15 mg/kg	12 h		
32–52 weeks' PCA	Oral	20 mg/kg	10–15 mg/kg	6–8 h	60 mg/kg	48 h
	Rectal	30 mg/kg	20 mg/kg	8 h		
>3 months	Oral	20 mg/kg	15 mg/kg	4 h	90 mg/kg	72 h
	Rectal	40 mg/kg	20 mg/kg	6 h		

PCA post-conceptual age

Table 15.5 Intravenous acetaminophen dosing guide[a]

Age	Drug	Loading dose mg/kg	Maintenance dose mg/kg	Dose interval
28–31 weeks' PCA	Acetaminophen	20	10	12 h
32–44 weeks' PCA	Acetaminophen	20	10	6 h
>44 weeks' PCA	Acetaminophen	15	15	6 h

[a] Adapted from [100, 107]

multiple roles in early development, and inhibition of their synthesis with NSAIDs may potentially result in disruption of the sleep cycle, an increased risk of pulmonary hypertension, alterations in cerebral blood flow, decreased organ perfusion and renal function, and disrupted thermoregulation [110].

In premature neonates in intensive care, prophylactic intravenous indomethacin reduces both the need for surgical ligation of patent ductus arteriosus and the incidence of grade 3 and 4 intraventricular hemorrhage. Reductions in cerebral, renal, and mesenteric blood flow velocity occur for 2 h after bolus indomethacin but can be minimized by continuous infusion. Renal effects are also less with the use of ibuprofen compared with indomethacin. There is therefore a potential to reduce NSAID-related adverse effects. More recently, oral acetaminophen has been shown to be as efficacious as ibuprofen for PDA closure but with a smaller risk of adverse effects [111–113].

Opioids

Morphine is the prototypic opioid, which has been relatively extensively investigated in the neonate. There is considerable clinical experience with morphine used to treat severe acute pain after surgery and in the NICU. Dose requirements and clinical responses to opioid analgesics differ markedly between premature and term neonates, infants, and children. There are multiple contributors to this difference including age-dependent changes in body composition and organ function influencing opioid pharmacokinetics and genetic and developmental factors that change opioid pharmacodynamics. Therefore, regular and serial assessments of pain after titrating and adjusting the opioid doses according to individual responses are required to achieve analgesia and minimize adverse effects. Tolerance leading to dose escalation and subsequent physical withdrawal response if opioid infusion rates are reduced too rapidly are distressingly frequent problems after medium- to long-term use in intensive care [114]. Other more lipophilic opioids such as hydromorphone, fentanyl, and remifentanil are also chosen to manage acute pain on occasion in neonates and are therefore discussed briefly below along with tramadol and the morphine prodrug codeine.

Morphine

Morphine can be given orally or parenterally. Morphine solutions are generally well absorbed orally, but the pharmacokinetics and efficacy of oral opioids have not been clearly established in neonates. Oral morphine can be given at an effect-titrated dose of 0.05–0.1 mg/kg every 4–6 h in carefully monitored non-ventilated term neonates (Table 15.6). However, a recent blinded randomized placebo-controlled trial (Poppi trial) investigating whether 0.1 mg/kg oral morphine provides effective analgesia for procedural pain (retinopathy of prematurity screening and heel lance) in non-ventilated premature infants [115] had to be terminated early due to profound respiratory adverse effects, without demonstrating analgesic efficacy [116]. The authors strongly advised caution when oral morphine is used for other acute painful procedures in non-ventilated premature infants.

Parenteral morphine is usually given intravenously either by intermittent dosing, continuous infusion, or in a nurse-controlled analgesia (NCA) regimen (Tables 15.6 and 15.7, Box 15.1) [117]. Subcutaneous morphine is also used. The pharmacokinetics and clinical use of morphine in neonates have been reviewed [118–121] (see Chap. 3). The pharmacokinetics of IV morphine are developmentally regulated, and the neonatal period is characterized by high interpatient variability [122] and reduced clearance, making the clinical effects of morphine less predictable than in older children. A pharmacokinetic model for children up to the age of 3 years, including premature neonates, showed that the capacity of morphine glucuronidation and the clearance of metabolites are influenced by body weight in a nonlinear manner [123]. The clearance and glucuronidation capacity of neonates 1–10 days of age is approximately 50% less than that of older infants and children, which are less than previously reported [121, 124]. Consequently, significantly smaller doses are advised, particularly in the premature neonate, than those generally recommended 10–40 mcg/kg/h [125]. Using a wider population, morphine clearance has been predicted across the entire pediatric age range [126], but further studies

Table 15.6 Morphine dosing and morphine infusion

Morphine dosing	
Preparation	
Oral solution	50–100 mcg/kg, 4–6 hourly
Intravenous	25–50 mcg/kg initial dose (titrated according to response)
	25 mcg/kg every 30 min to 1 h
Morphine infusion	
Preparation: Morphine sulfate 1 mg/kg in 50 mL solution	
Concentration	20 mcg/kg/mL (0.02 mg/kg/mL)
Initial dose	0.5–2.5 mL (0.01–0.05 mg/kg)
Infusion rate	0.1–0.6 mL/h (2–12 mcg/kg/h)

Table 15.7 NCA (morphine) protocol for neonates and infants

NCA[a] for neonatal use	
Preparation: Morphine sulfate 1 mg/kg in 50 Ml solution	
Concentration:	0.02 mg/kg/mL
Initial dose:	0.5–2.5 mL (0.01–0.05 mg/kg)
Pump programming	
Background infusion	0–0.5 mL (0–0.01 mg/kg/h)
NCA dose	0.5–1.0 mL (0.01–0.02 mg/kg)
Lockout interval	20 or 30 min

[a]NCA is a demand-led, flexible morphine infusion system using a PCA infusion pump [117]. It is suitable for neonates who are not receiving respiratory support provided they are closely monitored by appropriately trained staff

Box 15.1: NCA

NCA is a demand-led alternative for patients who are too young or unable to use PCA (patient-controlled analgesia). It is designed to provide safe, potent, flexible, and convenient pain control by combining the possibility of a continuous opioid analgesic infusion with on-demand bolus doses of analgesia administered according to predetermined limits. NCA was first developed for infants and those children and adults who were unable to operate the PCA handset and was subsequently adapted for neonates [117]. Suggested initial NCA infusion programming for a postsurgical neonate is shown in Table 15.7.

are required to correct for type of pain and severity of illness, in addition to differences in PK. The large variability in morphine clearance, particularly in critically ill neonates, may be attributed to variations in hepatic and renal functions and hepatic blood flow, type of surgery, and possibly genetic differences. Recently, the pharmacogenetic (PG) effects of variants at the loci of organic cation transporter 1 (OCT1) and UDP-glucuronosyltransferase 2B7 (UGT2B7) have been studied in critically ill neonates, and a PBPK model that accounted for OCT1 ontogeny and PG effect adequately described the observed variability in morphine PK [127, 128].

Although the plasma levels associated with analgesia are not well defined and a concentration-response profile is lacking [53], a mean steady-state serum concentration of 10 ng/mL is a reasonable target. This level was achieved in children in intensive care after noncardiac surgery with a morphine hydrochloride infusion of 5 mcg/kg/h at birth (term neonates), 8.5 mcg/kg/h at 1 month, 13.5 mcg/kg/h at 3 months, 18 mcg/kg/h at 1 year, and 16 mcg/kg/h for 1- to 3-year-old children [120]. Conversely, a common threshold for respiratory depression in neonates, infants, and children has been defined as 20 ng/mL [129]. Any differences in efficacy observed between continuous infusion and intermittent boluses of morphine probably relate more to the age-appropriate total dose of drug received, rather than the method of administration [130, 131]. Sedation and respiratory depression are the most frequently seen adverse effects of morphine (and other opioids); adverse effects of morphine can be reversed with the opioid antagonist naloxone.

Fentanyl

Fentanyl is a synthetic, high-potency (100 × morphine) lipid-soluble opioid. Its main use is for intraoperative analgesia where its rapid onset, short initial half-life, and its cardiovascular stability at larger doses are an advantage. It prevents pain-induced increases in pulmonary vascular resistance, causes less histamine release than morphine, and is therefore more stable in patients with congenital heart disease and chronic lung disease. Fentanyl is also used by infusion in NICU, and it has some advantages for procedural pain owing to its rapid onset. Administered as a bolus, fentanyl has been found to be safer than when administered by continuous administration [132], despite previous reports of a reduced frequency of apneic spells after continuous infusion compared with bolus administration [133]. Unfortunately, fentanyl has the potential for a more rapid development of tolerance with prolonged use because of the greater duration of receptor occupancy [134]. Opioid withdrawal syndromes can also occur.

After intravenous administration, the duration of a single dose of fentanyl is 30–45 min. As fentanyl is very lipophilic, its pharmacokinetic profile is context sensitive such that the half-life progressively increases with the duration of the infusion [135]. A predictive PKPD model of fentanyl that includes growth and maturation physiological changes in neonates has been developed [136]. High-dose fentanyl has been associated with chest wall rigidity [137] and subsequent difficulty in ventilation, and such doses are therefore usually only given when respiration is controlled [138]. It can also be given neuraxially; in the epidural space, it is used alone or in combination with local anesthetic by infusion after major surgery [139, 140].

Alfentanil and sufentanil are fentanyl analogs with different potencies and durations of effect. Their principal use is during anesthesia, but they have also been used for ongoing pain and pain due to brief procedures, particularly on ICU [141, 142]. Sufentanil is more potent (10 × fentanyl) [143] but otherwise very similar to fentanyl in clinical effect; it has been used for intubation [144] and by infusion in ICU but probably does not offer significant advantage. Alfentanil pharmacokinetics have been studied in the neonate [145, 146]. It is less potent than fentanyl and of relatively short duration after a single dose. It is also sometimes used to facilitate tracheal intubation [142]. However, like fentanyl, doses effective for painful procedures can lead to chest wall rigidity in neonates and again, therefore, should probably only be used if ventilation is controlled [147].

Remifentanil

Remifentanil is an ultrashort-acting fentanyl analog that is metabolized by tissue and plasma esterases. As a result, its elimination is therefore independent of liver and renal function. The context-sensitive half-life of remifentanil remains in the order of several minutes even after several hours of infusion, presenting obvious advantages in anesthesia and sedation practice. The use of remifentanil in neonates has been reviewed recently [148–150]. Given its rapid metabolism, the major advantage of remifentanil remains its ability to control the stress response during major surgery while permitting a rapid recovery. The pharmacokinetic principles apply across all age ranges including neonates.

Although remifentanil has been used during surgery and to sedate neonates ventilated in the NICU, the rapid development of tolerance and possibility of opioid-induced hyperalgesia (OIH) are potential problems. In a study that compared remifentanil- and fentanyl-based analgesia and sedation in 23 ventilated infants, the risk of tolerance, withdrawal, and OIH were not increased with the former [151]. It has even been used successfully at high infusion rates for laparotomy in extremely low birth weight premature neonates with necrotizing enterocolitis [152]. If remifentanil is used during anesthesia, then longer acting opioids are usually substituted immediately before or after awakening to prevent severe pain in the early postoperative period [153].

High infusion rates and large bolus dosing may result in hemodynamic instability (bradycardia and hypotension), particularly in premature neonates and in patients with cardiac dysfunction. This is usually easily treated with intravenous fluids or decreasing the infusion rate of remifentanil. Given its short context-sensitive half-life, it can be used effectively during surgery by starting at a low infusion rate and titrating up according to the hemodynamic responses [154]. Remifentanil is also used in other clinical scenarios including tracheal intubation, brief invasive procedures, or sedation during mechanical ventilation in the NICU. Chest wall rigidity is a potential adverse effect, particularly with large or rapid boluses as has been used for tracheal intubation. For example, bolus doses of remifentanil of 1, 2, or 3 mcg/kg resulted in rigidity in 6%, 10%, and 13% of the neonates, respectively [155–157]. The rate of administration and duration between repeat boluses may be important in reducing the risk of chest wall rigidity [158, 159].

Hydromorphone

Hydromorphone is a potent semisynthetic morphine derivative that is popular in pediatric practice. It is used extensively in PCA and epidural analgesia regimens in older children. Hydromorphone is approximately four to five times more potent than morphine and has a lipid solubility intermediate between morphine and fentanyl. It has no active metabolites, which is potentially an advantage in neonatal practice, but its use has not been well described or studied in this age group.

Codeine

Codeine is a low-potency opioid that until recently has been popular in pediatric practice for the treatment of mild to moderate severe pain. Codeine is a morphine prodrug; about 10–15% of each dose of codeine is metabolized to morphine by the cytochrome P450 enzyme CYP2D6, and the morphine metabolite is thought to be responsible for codeine's analgesic effect as analgesia cannot be demonstrated in human volunteers when the pathway is pharmacologically blocked. CYP2D6 activity is genetically regulated; 5–40% of individuals in some populations have reduced, little, or no activity ("slow and intermediate metabolizers") and consequently are less able to produce morphine from codeine, leading to unpredictability of effect [160]. Conversely, "rapid metabolizers" may experience adverse effects from excess morphine resulting in unexpected respiratory depression [161]. Several children with obstructive sleep apnea who received codeine for pain post-adenotonsillectomy were found dead and subsequently found to be rapid metabolizers [162, 163]. This led to a proscription of codeine in young children in the USA. In contrast, institutions that genotyped children for 2D6 polymorphisms continue to use codeine safely in children by avoiding its use in rapid and poor metabolizers [164]. Moreover, CYP2D6 activity is developmentally regulated, with lower levels in the very young [165].

Traditionally codeine was chosen where respiratory depression, sedation, or other opioid-related side effects were a particular concern, e.g., the neonate and after neurosurgery, but the use of codeine for these indications was challenged because of uncertainties regarding its efficacy and safety [161]. Regulatory agencies such as the Medicines and Healthcare Products Regulatory Agency (MHRA), the Food and Drug Administration (FDA), and the European Medicines Agency (EMA) no longer recommend its use in children under 12 years.

However, codeine still features in the management of pain in breastfeeding mothers leading to concerns for potential toxicity in neonates including central nervous system depression and death [166–168]. To ensure neonatal safety, it is important to follow evidence-based guidelines [169]. Genotyping the mothers may prove useful in improving the outcome of codeine therapy in this setting [170, 171].

Tramadol

Tramadol is a synthetic opioid analgesic that also inhibits serotonin and norepinephrine reuptake [172]. It has been used widely for acute and chronic pain in children, and there is an extensive body of literature describing its efficacy and indications. Like codeine, tramadol is metabolized by the cytochrome enzyme CYP2D6 to its major active metabolite o-desmethyltramadol, which has a 200 x increased affinity for the mu opioid receptor. CYP2D6 is genetically and developmentally regulated (as is codeine metabolism above), which may have implications for the use of tramadol in very young patients. The effect of CYP2D6 polymorphism on the efficacy and disposition of tramadol is not known. The pharmacokinetics of tramadol in neonates and infants has been investigated, no relationship between post-menstrual age and o-desmethyltramadol production was established, maturation of tramadol elimination occurs early (50% of adult value at term gestation) [173], and clearance reaches 80% of adult values by 1 month [174, 175].

Opioid side effects are less prominent with tramadol, but this was not confirmed when equianalgesic doses were used

[172, 176]. Although a randomized trial of fentanyl (1–2 mcg/kg/h intravenously) or tramadol (0.1–0.2 mg/kg/h intravenously) in neonates in the first 72 postoperative hours reported equianalgesic efficacy for the two drugs, tramadol offered no advantages over fentanyl in terms of the duration of mechanical ventilation and the time to reach full enteral feeds [177]. In another randomized trial in postsurgical neonates, the addition of tramadol to a standard analgesic regimen of intravenous acetaminophen and a morphine infusion did not affect the time to extubation, morphine or midazolam exposure, or pain scores [178]. This study questioned the benefit of using tramadol in postsurgical neonates, although the effects of tramadol in this study may have been masked in part by the dose of morphine [179]. Conclusions about the safety of tramadol in the neonate are limited by the small size of the PKPD data available.

In 2017, the FDA recommended that tramadol should not be used in the management of pain in children under 12 years old and breastfeeding mothers due to the risk of serious adverse reactions. However, to date, no deaths have been reported in breastfed neonates whose mothers used tramadol (National Library of Medicine. Drug and Lactation Database (2016)) nor have deaths been reported in neonates associated with therapeutic tramadol [180].

It has been recommended that tramadol dose should be limited for acute pain after tonsillectomy (e.g., maximum dose 1 mg/kg 6–8 h, maximum 400 mg/day) and starting with a smaller dose of 2 mg/kg daily in divided doses (e.g., 0.5 mg/kg 6–8 h) [181]. A comprehensive summary of the literature has been published, and the authors suggest that the recommendation to avoid tramadol when breastfeeding and the contraindication to use in children (including neonates) is inappropriate and recommendations should instead focus on seeking medical advice and dose adjustment if sedation is experienced in the mother or suspected in the breastfed infant [168, 180].

Non-opioid Analgesics

Clonidine and Dexmedetomidine

Clonidine and dexmedetomidine are alpha$_2$ adrenergic agonists capable of producing analgesia both systemically and neuraxially. Clonidine has analgesic, sedative, and antiemetic properties; it can also cause hypotension and bradycardia. It is used as a sedative infusion in ICU areas and for the symptomatic treatment of effects due to the rapid withdrawal of opioid analgesics [182]. Both agents have been found to have opioid-sparing effects when used as adjuncts to sedation and analgesia in neonates [183]. Clonidine infusions at 1 mcg/kg/h in ventilated neonates reduced fentanyl and midazolam requirements with deeper levels of analgesia and sedation without substantial side effects [184]. When clonidine (in doses of 0.5–2 mcg/kg/h) was used to sedate small infants after cardiac surgery, it proved to be hemodynamically safe, with a maximum decrease in mean HR of only 12% and transient and limited decreases in diastolic blood pressure of 13% [185]. These findings were confirmed in a second study that used clonidine infusions in infants after cardiac surgery [186]. However, a Cochrane Database systematic review found insufficient evidence to confirm the safety and efficacy of clonidine for sedation and analgesia in term and preterm infants who were mechanically ventilated [187].

Dexmedetomidine sedation and caudal epidural anesthesia have been used successfully for lower abdominal and lower limb surgery in ex-preterm and term infants with severe comorbidities [188]. In a pilot study, dexmedetomidine at 2 mcg/kg over 10 min, followed by 1 mcg/kg over the next 10 min, was used to sedate infants to place a caudal block for an inguinal hernia repair [189]. A meta-analysis of perioperative analgesic effects in children, infants, and neonates showed intraoperative dexmedetomidine reduced postoperative opioid requirements and pain intensity without effect on the frequency of postoperative nausea and vomiting. The optimal bolus was 0.5 mcg/kg or more [190].

Dexmedetomidine has not been associated with neuroapoptosis or other neurodegenerative effects in animal studies involving infant rodents and fetal primates [191] and attenuates isoflurane-induced neurocognitive impairment in neonatal rats [192]. The areas of the brain affected by dexmedetomidine (primary sensory brain region) are different from ketamine (limbic brain regions) [193]. The bulk of present evidence suggests fewer consequences attributable to alpha$_2$ agonists than most other anesthetic drugs [194].

Pharmacokinetic data for dexmedetomidine are limited in neonates and infants.

In a phase II/III safety, efficacy, and PK study of dexmedetomidine in 18 mechanically ventilated term neonates receiving dexmedetomidine 0.05–0.2 mcg/kg/h, clearance was 0.9 (0.2–1.5) L/kg/h and even less in 24 premature neonates (0.3 L/kg/h) [195]. Dexmedetomidine undergoes almost complete hepatic transformation, and so these lower clearances are likely to reflect their decreased hepatic enzyme activity compared with adults [196]. In an open-label single-center PK study, younger infants (with a PMA of 33–61 weeks and a body weight of 2–6 kg) and those with a history of cardiac surgery were significant predictors of reduced clearance and may therefore require relatively lower doses to achieve exposure similar to older patients [197]. There were no significant associations between dexmedetomidine concentrations and hypotension. In a PK study in 23 neonates and 36 infants after open heart cardiac surgery, continuous infusions of up to 0.3 mcg/kg/h in neonates and 0.75 mcg/kg/h in infants were well tolerated [198]. It has found a niche in critically ill neonates and infants with congenital heart disease because of its minimal effects on respiratory function at sedative doses, facilitating early extubation and fast-track

postoperative care. However, there is a potential risk for withdrawal seizures after dexmedetomidine sedation for cardiac surgery, particularly with greater cumulative doses and abrupt discontinuation [199].

Neonates appear to be more susceptible to the effects of clonidine including side effects. After severe delayed respiratory depression was reported in a neonate given 2 mcg/kg caudal epidural clonidine, several similar cases were published resulting in a warning of caution in neonates for all routes of administration [200–203]. Epidural dexmedetomidine analgesia was also found to be developmentally regulated and relatively greater in neonates in a rodent laboratory model and may be better tolerated, but when administered caudally in children it showed no advantages over clonidine, and there has been limited spinal safety evaluation [204, 205].

Ketamine

Ketamine is a glutamate NMDA receptor antagonist that produces a state of "dissociative" anesthesia. It has been used for many years as an intravenous general anesthetic with several advantages: profound analgesia, relative preservation of respiration and respiratory reflexes, and cardiovascular stimulation. At low doses (<1 mg/kg), it is an effective analgesic; in particular, it appears to reduce the hypersensitivity due to central sensitization after injury or surgery in both inflammatory and neuropathic conditions. Although numerous publications describe the analgesic effects of ketamine, a systematic review concluded that its role in the management of postoperative pain in the adult remains unclear [206]. Ketamine has been effective in resetting opioid requirements in patients who chronically abused opioids. The disadvantages of ketamine include infrequent emergence phenomena such as hallucinations and unpleasant dreams and nausea and vomiting.

The NMDA receptor is known to undergo developmental changes in distribution, structure, and function and is thought to be important in regulating neuronal plasticity during the developmental period [3]. The precise impact of this on the efficacy or toxicity of ketamine (or other NMDA antagonists) in neonates is still not fully understood. The principal uses of ketamine in neonates include for intravenous induction of anesthesia in high-risk patients with cardiovascular disease and for procedural sedation. The potential for neurotoxicity from systemically or spinally administered NMDA antagonists is also a concern that is widely debated [207, 208]. Systemically administered ketamine, and a number of other substances including some sedatives and anesthetic agents, can produce damaging neurodegeneration in rodent brains during a critical period of rapid synaptogenesis in the early postnatal period [209] (see Chap. 18). Ketamine has more recently been found to alter neurogenesis from neural stem progenitor cells in the developing rat brain [210]. Early studies in primates indicate that similar histological damage is possible but critically dependent on age at exposure, drug dose, and duration of treatment, with the greatest risks being inter-utero and in the first few days of life [211]. The role of ketamine varies not only on the basis of the dose and frequency of exposure but also the intensity of the noxious stimuli [212]. Repeated ketamine usage may be neurotoxic to immature brains in the absence of noxious stimuli, whereas it may be neuroprotective in the same brains in the presence of strong painful stimuli [213, 214]. The significance of these findings in humans and implications for clinical practice are not known [215]; however, taken together, they raise concern regarding the use of ketamine in premature infants and term neonates [208].

Spinally (epidural) preservative-free ketamine has not been clinically implicated as a cause of neurotoxicity, although recent research in rodents has led to a conclusion that the benefit-risk ratio is unlikely to be favorable in neonates and young children and so it should be avoided [200, 216].

Local Anesthetics

LA is very important in infant acute pain management, particularly during and after surgery and for procedural pain where opioid requirements and opioid-induced side effects such as depression of respiration can be reduced or avoided by the use of LA. Topical LA, LA infiltration, and peripheral and central regional analgesia are all used extensively for acute pain indications in neonates. The detailed pharmacology of local anesthetics and regional anesthetic techniques are detailed in Chaps. 3 and 16.

Lidocaine, Bupivacaine, Levobupivacaine, Ropivacaine, Chloroprocaine

The amide-type LAs lidocaine and bupivacaine have been the most commonly used in neonates for several decades, and there is considerable clinical experience of their efficacy and safety at all ages. Lidocaine has a rapid onset and is of short to intermediate duration; it is used for local infiltration and regional nerve blocks, particularly where a rapid response is required. EMLA (eutectic mixture of local anesthetics) is a combination of lidocaine and prilocaine for topical analgesia – see below for a detailed description. Bupivacaine has a slower onset and long duration, 4-h analgesia or longer can be expected after a single dose in a central nerve block, and consequently it has been the first choice for postoperative analgesia. Their pharmacology and pharmacokinetics have been well investigated and reviewed [217]. Bupivacaine is a racemic mixture. The S(+) enantiomer, levobupivacaine, has a slightly improved in vivo and in vitro safety profile compared to bupivacaine but is otherwise similar [218, 219]. Ropivacaine is an amide LA with similar clinical properties to bupivacaine except that motor block is slower in onset, less intense, and shorter in duration [200]. Ropivacaine and its active metabolite 2′,6′-pipecoloxylidide (PPX) unbound clearance depends on body weight and age [220]. Ropivacaine may have theoretical advantages during prolonged infusion in neonates and

infants as unlike bupivacaine context-sensitive half-life does not increase with increased duration of infusion [200]. Most recently, 2-chloroprocaine has seen a resurgence in use in neonates and premature infants for caudal blocks in awake neonates for open (and closed) hernia repair and lower abdominal surgery [221, 222]. Since chloroprocaine is spontaneously degraded by plasma esterases, it has a very brief half-life even in neonates with reduced pseudocholinesterase activity. This precludes accumulation of the local anesthetic and reduces the risk of toxicity even after prolonged regional blockade.

Toxicity of LAs depends on the age of the patient, the local anesthetic, dose, and route of administration. Neurotoxicity and cardiotoxicity have been reported in neonates who have a reduced threshold for toxicity, but provided the recommended doses are observed, toxic events are rare [223]. LAs are extensively protein bound (>90%), with the free, unbound, fraction being the pharmacologically active fraction. AAG (alpha-acid glycoprotein) and albumin are the most important plasma proteins that bind drug; AAG concentrations in the blood are reduced in the neonate resulting in increased unbound fractions of lidocaine and bupivacaine [224]. Plasma bupivacaine concentrations >3 mcg/mL are associated with neurotoxicity in the awake adult and cardiotoxicity >4 mcg/mL; the equivalent concentrations in neonates are unknown, although toxicity has been reported after bupivacaine infusions at doses >0.3 mg/kg/h, leading to a reduction in recommended doses and infusion durations in the neonate to ≤0.2 mg/kg/h [225]. When transversus abdominis (TAP) blocks were performed in ten neonates using 1 mL/kg or 0.125% levobupivacaine, the greatest plasma concentration, 0.26 mcg/mL, was significantly less than the potentially toxic plasma threshold (1.5–2 mcg/mL) suggesting a low risk of LA toxicity [226]. In contrast to bupivacaine infusions, plasma concentrations after ropivacaine infusions in infants <1 year did not continue to increase with time, although absolute concentrations and free fraction were similarly increased at younger ages [227]. In a comparison of epidural bupivacaine and ropivacaine, boluses and infusions in neonates and young infants showed that epidural infusions of 0.2 mg/kg/h bupivacaine or ropivacaine were well tolerated and efficacious with no accumulation of unbound drug [228]. 2-Chloroprocaine overdose has not been reported in neonates or older infants.

Intralipid 20% has been used to treat inadvertent local anesthetic toxicity of amide local anesthetics in neonates and children [229]. This lipid emulsion is distinguished from propofol, which is an emulsion of a general anesthetic in a 10% suspension of long-chain triglycerides that should *not* be used for said purpose. Although a dosing regimen for Intralipid to treat local anesthetic toxicity in neonates has not been forthcoming, titrating doses of 1 mL/kg Intralipid and monitoring the circulatory responses until a stable rhythm is re-established appears to be a sensible approach at this time (see Chap. 16).

EMLA, Amethocaine Gel, and Other Topical LA Preparations

Topical LA has revolutionized the practice of minor needle-related procedures such as venipuncture, venous cannulation, and lumbar puncture [230]. A number of preparations are available, and the most frequently studied and in clinical use are EMLA and Ametop (amethocaine gel).

Lidocaine forms a eutectic mixture with prilocaine such that the combination has a lower melting point than either of the constituents. This mixture, formulated as a cream, can produce LA when applied to intact skin. When applied for about 60 min under an occlusive dressing, the duration of the resulting cutaneous analgesia is several hours. EMLA is suited for use in the neonate in single doses; multiple doses should be limited to a maximum of four applications per day and under close supervision to preclude methemoglobinemia. Measurement of blood methemoglobin concentrations has been advised if multiple applications or large doses of EMLA are applied [231, 232]. A metabolite of prilocaine, o-toluidine, can increase the blood levels of methemoglobin, an oxidized form of hemoglobin which has a reduced oxygen-carrying capacity. Methemoglobin reductase, the enzyme which catalyzes reduction to hemoglobin, is also developmentally regulated, rendering neonates susceptible to methemoglobinemia because fetal hemoglobin is more easily oxidized [233]. Minor side effects of transient paleness or redness and edema of the skin may occur following application. Tetracaine is a potent ester-type LA. Due to its high systemic toxicity, it is only used for surface anesthesia (not on mucus membranes), with about 15% bioavailability after application to intact skin.

Four percent tetracaine gel (Ametop) produces surface anesthesia in about 30 min with an absorption and elimination half-life of about 75 min. Its duration of analgesia is 4–6 h. Ametop therefore produces a more rapid onset of action and greater duration than EMLA. It has been shown to be effective in the neonate [234]. Mild erythema at the site of application is seen frequently but of little consequence; edema of the skin, itching, and even blistering have been reported in older children but are rare in the neonate.

Sucrose

Sucrose solutions may reduce physiological and behavioral signs of pain in neonates during brief painful procedures such as heel lance blood sampling [235].

Volumes of 0.05–2.0 mL of a 12–24% solution of sucrose administered 1–2 min before a painful stimulus appears to be effective [235, 236]. It can be administered using a pacifier or dripped directly onto the tongue using a syringe, with the number of drops titrated to the infant's response. Coughing, choking, gagging, and transient oxygen desaturation can

occur. The safety of multiple administrations in very small premature infants has been questioned as changes in neurobehavioral responses were observed after repeated sucrose administration in this group [237, 238].

It is important to note however that sucrose has not been found to significantly affect activity in neonatal brain or spinal cord nociceptive circuits, suggesting that it should not be considered an effective analgesic drug [239]. There was also no difference in the cortical response to pain during venipuncture in neonatal infants who were administered sucrose versus those who were breastfed [240].

Postoperative Pain Management

Postoperative pain management should always be planned before beginning surgery [241]. Initiation of postoperative pain relief is usually considered to be part of the plan of anesthesia; patients should not normally be discharged from the PACU (postanesthesia recovery unit) or returned to the ICU until they are comfortable, and an ongoing pain management plan is established. Pain management protocols should include pain assessment, monitoring, criteria for additional analgesia, management of side effects, and criteria for transition to simpler, usually oral, analgesia when appropriate. Neonatal surgery may be relatively minor, such as circumcision or uncomplicated inguinal hernia repair on otherwise well neonates, or major interventions in life-threatening circumstances carried out on very sick infants. Appropriate analgesia depends on the exact prevailing circumstances, which depends on the type of surgery, physical state of the child, and available facilities for postoperative care and level of staff training. Some of the more commonly encountered procedures, divided into three groups of increasing complexity, are listed in Table 15.8. Conventionally, analgesia is commenced intraoperatively as part of the plan of anesthesia using combinations of local anesthetics, opioids, and acetaminophen and suitable ongoing analgesia administered orally, rectally, or parenterally as indicated.

Table 15.8 Common surgical procedures

Neonatal surgery
Group 1
Inguinal hernia repair
Pyloromyotomy
Orchidopexy, orchidectomy
Group 2
Duodenal atresia
Intestinal malrotation
Colostomy formation
Urogenital malformations
Group 3
Bowel resections NEC
Esophageal atresia
Congenital diaphragmatic hernia
PDA repair
Congenital heart surgery

Group 1: Inguinal Hernia Repair, Circumcision, Pyloromyotomy, etc.

Neonates presenting for this type of surgery are usually healthy. The surgeries are generally relatively brief and are sometimes performed using minimally invasive laparoscopic techniques.

LA: Caudal epidural analgesia or simple LA nerve blocks such as ilioinguinal block and penile block are often indicated. If these techniques are not suitable, then subcutaneous infiltration at the surgical incision or laparoscope port sites with a relatively long-acting LA such as levobupivacaine is an option.

Opioid analgesia: Fentanyl or other suitable intravenous opioid administered as part of anesthesia can be continued into the postoperative period if necessary. Oral intake is usually rapidly resumed, therefore oral morphine solution can be given every 4 h as required. However, it is unusual for neonates to require more than one or two doses following this group of procedures.

Acetaminophen: A loading dose should be administered during surgery; it is convenient to give it intravenously. Oral and rectal dosing are options; the first dose can be given prior to surgery, but rectal absorption is less predictable in neonates. Acetaminophen can be continued orally at appropriate doses for 2 or 3 days as needed.

Group 2: Major Gastrointestinal or Genitourinary Surgery

Although surgery can be quite prolonged and relatively invasive, the majority of neonates presenting for these procedures are well and can be expected to recover rapidly. A potential problem is that high doses of intraoperative opioid may be required to obtund physiological responses to surgery leading to delayed recovery and possibly necessitating postoperative respiratory support.

LA: Continuous epidural analgesia should be considered for this group as it allows early postoperative tracheal extubation and reduces the need for ongoing respiratory support.

Opioid: High-potency analgesics such as parenteral opioids or local anesthetic infusions may be needed as part of a "balanced analgesia" approach. Intravenous opioid infusion may be needed postoperatively, and NCA (see above) should be considered because it is easier to adapt dose requirements to individual patients and circumstances.

Acetaminophen: It is somewhat unclear whether acetaminophen significantly contributes to analgesia in conjunction with these more potent analgesic techniques although a recent systematic review concluded that it might reduce morphine requirements after major surgery [242]. Rectal acetaminophen did not reduce morphine requirements in neonates after major abdominal surgery in one study [89]. But as rectal absorption is unreliable and pain assessment is difficult in these infants, further study would be required before firm conclusions can be drawn. Acetaminophen, and particularly intravenous acetaminophen, should not be given at full dose for more than a few days because of potential toxicity, and therefore its use may usefully be delayed until epidural or IV opioid infusions are being withdrawn following the second or third postoperative days.

Group 3: Cardiothoracic Surgery or Complex Gastrointestinal/Genitourinary Surgery

These infants are frequently unwell, in poor clinical condition, or critically ill. Sepsis, cardiorespiratory insufficiency, and significant blood loss can complicate the perioperative period. Few of these neonates are extubated within the first postoperative day. Preterm neonates with necrotizing enterocolitis who need GI surgery or ventilator-dependent neonates with PDA are often too immature or too unwell to tolerate procedures such as placement of an epidural unless strongly indicated. Potent intravenous opioid analgesia by continuous infusion or NCA with or without acetaminophen is the mainstay of analgesia in this group. Neonates having surgery for NEC need greater doses of morphine postoperatively than neonates operated on for other conditions [243]. Postoperative pain management after cardiac surgery in neonates has previously been reviewed [244].

Analgesia for Neonates in ICU

The EUROPAIN study of 6680 neonates in 243 NICUs in Europe showed wide variations in sedation and analgesia practices among NICUs [84]. Neonates who have undergone surgery require analgesia; this is usually given in the form of an opioid infusion in ICU settings. Preterm and other neonates in ICU who need respiratory support may also require pain relief, but there is ongoing and presently unresolved debate regarding whether the use of opioid infusions in neonates who are ventilated in ICU should be routine. Typically, these infants undergo numerous painful medical procedures such as heel lance blood sampling, insertion of arterial lines, lumbar puncture, and many others, and in addition the presence of the endotracheal tube may itself be painful. Aside from humanitarian and ethical reasons for giving analgesia, routine use of morphine infusions has improved cardiorespiratory stability in ventilated neonates and possibly neurological outcome [245]. However, this benefit was not confirmed in a subsequent large study, which initially reported an association between bolus morphine administration and worse outcome [246]. Reanalysis of those data demonstrated that poor neurological outcomes were related to preexisting hypotension and morphine therapy was not a contributory factor [247]. However, morphine infusions can produce hypotension, and the safety, efficacy, and long-term outcomes of analgesia and sedation in ventilated neonates require further evaluation. A follow-up study of ventilated preterm neonates who were randomized to either morphine or no morphine failed to show any serious long-term consequences in the neonates who received morphine [248]. In contrast, midazolam, frequently used for sedation in older patients in intensive care, has been strongly associated with an increased incidence of poor neurological outcome in neonates [245]. Midazolam exposure was associated with macro- and microstructural alterations in hippocampal development of premature neonates and poorer outcomes consistent with hippocampal dysmaturation. The authors cautioned the use of midazolam in preterm neonates, particularly those not undergoing surgery [249]. A Cochrane Systematic Review including three trials (148 neonates) reported a greater incidence of adverse neurological events at 28 days' postnatal age (death, grade III or IV IVH or PVL) with midazolam compared with morphine infusions (RR 7.64, 95% CI 1.02 to 57.21; RD 0.28, 95% CI 0.07 to 0.49; NNTH 4, 95% CI 2 to 14, one study, 46 infants) [250]. The group concluded that data was insufficient to promote the use of intravenous midazolam infusion as a sedative for neonates undergoing intensive care, and the review raised concerns about the safety of midazolam in neonates. It behooves us to carefully assess the risk/benefit ratio of such drugs in neonates to avoid adverse sequelae. Although there is presently insufficient evidence to support the routine use of opioid infusions in ventilated neonates, morphine appears to be safer than midazolam to sedate neonates [251]. As the risks involved are often subtle and difficult to measure and their mechanisms not well understood, the selective use of opioids based on the assessment of pain, clinical judgment, and the present best available evidence has been recommended [252, 253]. It may be that the concomitant use of dexmedetomidine infusions confers benefits in terms of reduced sedation requirements and earlier introduction of enteral feeding, but this notion requires further study [254].

Procedural Pain

A number of documents including reviews, guidelines, and policy statements have been published on the subject of procedural pain management in the neonate [51, 255–260].

Table 15.9 Procedural pain management

Procedural pain management*
1. Consider if the planned procedure is necessary and how the information it will provide might influence care
2. Are available analgesics and pain management strategies likely to provide adequate pain relief? Is sedation or general anesthesia indicated?
3. Avoid multiple procedures if possible. Cohorting several procedures may be less stressful as long as effective analgesia is provided
4. Consider if modification of the procedure would reduce pain, e.g., venipuncture is less painful than heel lance
5. Allow sufficient time for analgesic drugs and other analgesic measures to be effective
6. Ensure that appropriate personnel are available and enlist experienced help when necessary
7. Formulate a clear plan of action should the procedure fail or pain become unmanageable using the techniques selected

*Adapted from [241]. A guideline from the Association of Paediatric Anaesthetists of Great Britain and Ireland

Analgesia for neonatal procedural pain has been relatively well studied, yet it is clear that many procedures are often poorly managed [28]. Painful procedures include blood sampling, insertion of intravenous and intra-arterial catheters, retinal laser treatment, insertion and removal of chest tubes, and endotracheal intubation, among others. In some cases, procedures are performed on neonates that would always entail general anesthesia in older children and adults; this is not consistent with evidence of increased sensitivity to nociceptive pain (see above) at this age. General considerations regarding procedural pain management are given in Table 15.9. Procedural pain management should include both appropriate pharmacological and non-pharmacological strategies whenever possible. LA and systemic analgesia may be appropriate, but acetaminophen has not been shown to be effective for procedure pain [242]. Non-pharmacological strategies might include, for example, breastfeeding during the procedure [261–263]. NNS, sucrose, or other sweet solutions are effective in term and preterm infants, and tactile stimulation and kangaroo care (skin-to-skin contact) are useful strategies for brief procedures in premature neonates [263–265]. However, oral sucrose does not significantly affect activity in neonatal brain or spinal cord nociceptive circuits and therefore might not be an effective analgesic drug per se, and the ability of sucrose to reduce clinical observational scores after noxious events in newborns should not be interpreted as pain relief [239]. A more recent RCT showed no difference in cortical responses to pain during venipuncture in neonates who were administered sucrose vs. those who were breastfed [240].

Published guidelines have reviewed the evidence for the effectiveness of pharmacological treatments for specific procedures, e.g., LA or opioids, and they should be consulted to inform locally developed protocols [241, 256, 259, 260, 266].

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Regional Anesthesia for Neonates

16

Adrian Bosenberg

Introduction

Although technically challenging in neonates, regional anesthesia has wide ranging benefits. Effective pain relief after surgery plays a significant role in the surgical outcome. Most major surgery is performed in the first few days of life – a time when critical physiological transitions are taking place. The challenge is to provide safe and effective analgesia [1–3].

Even though it may be impossible to completely eliminate postoperative pain particularly in spontaneously breathing neonates, much can be done to reduce the intensity of pain. Traditionally, intravenous opioids have been the primary therapeutics to blunt the stress response and provide analgesia [4]. However, these analgesics may require ventilatory support and monitoring in an intensive care unit. In contrast, regional anesthesia is the closest intervention to achieving complete analgesia in both ventilated and spontaneously breathing neonates without requiring either ventilatory support or intensive care admission [1–5].

Most regional blocks are placed during general anesthesia to ensure an immobile patient. In specific situations, however, spinal blocks [6–9], caudal blocks [7], epidurals [10, 11], caudal catheters [12], and peripheral nerve blocks [13, 14] have been placed while the neonates were "awake." However, sedation or conversion to general anesthesia is generally required for major abdominal or thoracic surgery [7, 10, 11].

Specialized equipment is required to perform regional anesthesia in neonates [2, 15, 16]. Portable high frequency ultrasound has improved our ability to place epidural and peripheral nerve blocks safely and with greater efficacy in children. Neonates are ideal subjects for ultrasound-guided blocks [17, 18] given that most peripheral nerves are superficial and the nerves and surrounding structures can be readily defined. Even the spinal cord can be visualized in neonates, since ossification of the vertebrae is limited [17, 18]. Despite these innovations, overall experience with neuraxial blocks in neonates remains relatively limited (Table 16.1).

Table 16.1 Neonatal epidural risk based on data accumulated from publications worldwide. Caudal catheters are included

Author	Number of institutions	Number cases	Complications	Ref
Murrell (1992)	Sydney Australia 1	20	0	[36]
Van Niekerk (1990)	Utrecht Netherlands 1	20	V 1	[73]
Bosenberg (1998, 2005)	South Africa 2	240, 11, 35	DP 1, C 1, V 1	[35, 52, 76]
ADARPEF (1994)	France Belgium Italy 38	43	0	[64]
Yamashita (1992–2000)	Japan 1	950	DP 7	[68]
Webster (1992)	Ontario Canada1	18	V 2	[200]
Williams (1995)	Vermont 1	17 with spinal	0	[37]
Courreges (1996)	France 1	45	0	[72]
Tobias (1999)	Columbia USA 1	25	0	[105]
Hasan (1994)	London 1	12	0	[70]
Vas (1999, 2001,2003)	Bombay 1	20	0	[71]
National UK audit (2007)	UK 21	529	C 1 DE 3	[63]
Frawley (2000)	Melbourne Australia 1	50 with spinal	0	[256]
Somri (2007)	Israel 1	24 with spinal	0	[11]
Valairucha (2002)	Boston 1	115 caudal cath	A-1	[171]

(continued)

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Table 16.1 (continued)

Author	Number of institutions	Number cases	Complications	Ref
Krishnan (2006)	Birmingham 1	20	0	[53]
Willschke (2007)	South Africa 1	85, 20	0	[17]
Raghavan (2008)	Birmingham 1	22	0	[47]
Schenkman (2009)	Israel 1	44	V 5 M1	[54]
Kost-Byerly (2002–2007)	Baltimore USA 1	23	0	[174]
Bailey (2001–2002)	Philadelphia USA 1	28 caudal cath	0	[212]
PRAN (2007–2014)	USA 20	307 caudcath 167	DP 2 V 6 A 1	[7]
ADARPEF (2010)	France, Tunis, Quebec, Swiss, Belgium 45	46	DP 1	[65]
Willschke et al. (2010)	Vienna 1	20	0	[10]
Martin	Seattle	20	0	[4]
Total	~102 institutions	2811	DP11 DE 3 C2 V 15 M 1 A 2	

DP dural puncture, *V* intravascular, *S* total spinal, *B* bloody tap, *DE* drug error, *H* hypotension, *C* convulsion, *M* meningitis, *A* aberrant presacral placement

Risks and Benefits

Before implementing any new pain management strategy, the risks and benefits of that strategy must be carefully evaluated to ensure the benefits do outweigh the risks and to avoid exposing the neonate to complications and adverse events [1, 2]. Potential benefits of regional anesthesia must also be weighed against a provider's ability to perform the block successfully as well as the ability of the staff to manage continuous infusions of local anesthetics and/or opioids safely.

Benefits: Surgically induced pain causes a spectrum of autonomic, hormonal metabolic, immunologic/inflammatory, and neurobehavioral consequences that may have detrimental effects [2, 19–25]. Acute pain can also have negative physiological consequences that include depressing respiration and systemic and pulmonary vasoconstriction that negatively influence compromised or immature organ function [2, 19–22].

In the late 1980s, Anand et al. first demonstrated that neonates, including preterm infants, are capable of mounting both hormonal and metabolic stresses in response to surgery [19]. They demonstrated that opioids inhibit the stress response to surgery. Regional anesthesia has been shown to inhibit the hormonal stress response more effectively than opioids [21, 23, 24]. The stress response also varies directly with the degree of surgical stress [2, 19] and is activated even by minor surgery. Thus, all neonates require a strategy to attenuate the nociceptive responses after surgery. There is also some evidence that severe stress may be pathological and increase postoperative morbidity and mortality with extreme catecholamine responses associated with worst outcome [2, 16]. Hence, regional anesthesia is particularly suited to attenuate the stress response and reduce adverse outcomes associated with opioid administration in neonates.

Neonates, and in particular preterm infants, exposed to the deleterious effects of pain are also at risk of neurodevelopmental impairment and altered pain sensitivity [26–31]. Long-term effects may include emotional, behavioral, and learning disabilities. In theory, regional anesthesia may avoid or, when used in combination with anesthesia, attenuate the neurotoxicity associated with general anesthetics [4, 28–31] when administered to newborn rodents and primates. The GAS (General Anesthesia and Spinal) study, which compared the neurodevelopmental outcome in young children at 2 and 5 years after either a general or spinal anesthetic, found similar outcomes with the two anesthetic techniques [32, 33].

There are additional advantages that should be recognized when regional and general anesthesia are combined in neonates [2, 5, 17, 34, 35]. As a distinct population, neonates are vulnerable to the effects of general anesthesia given their immature cardiovascular, central nervous, and respiratory systems, which are very sensitive to the depressant effects of general anesthetics. Neonatal myocardial function is particularly sensitive to both inhalational and intravenous anesthetics. When combined with general anesthesia, regional anesthesia provides profound analgesia with minimal hemodynamic effects [8], even in those with congenital heart disease [3, 35, 37–48]. A successful regional block reduces the concentrations of inhalational agents needed to achieve a successful outcome [3–5, 35], thereby attenuating the severity of cardiovascular and respiratory depression [3] and facilitating emergence and recovery. Inhalational agents also provide a reciprocal protective effect by increasing the threshold for local anesthetic toxicity [49].

Regional anesthesia also reduces the requirement for muscle relaxants by providing a degree of motor blockade. Neuraxial blockade facilitates the reduction of abdominal organs in gastroschisis [47], omphalocele, and diaphragmatic hernia [29, 38] by providing analgesia and relaxation of the abdominal musculature, independent of the mode of ventilation [5, 6, 35, 37]. Similarly, caudal blocks facilitate reducing incarcerated inguinal hernia before surgery, restoring blood flow to ischemic bowel or preventing ischemia of the bowel until surgery can be performed [44].

Neuraxial anesthesia may stimulate respiration and alter respiratory mechanics. [50, 51]. The effects of neuraxial blockade on ventilation depend on the level and intensity of the block, as well as the clinical scenario. Neuraxial blockade may diminish abdominal and intercostal muscle activity, particularly in the compliant chest wall of neonates. Alternately, blockade may improve diaphragmatic activity and excursion, thus offsetting a loss of accessory muscle function [36–38, 40]. The ventilatory response to CO_2 is also improved with a regional block, improving the efficiency of ventilation so that normocapnia can be maintained [50, 51, 54, 55]. The pain relief provided by epidural analgesia improves ventilatory mechanics [37, 47, 51] and reduces the need for and duration of assisted or controlled ventilation after major abdominal or thoracic surgery [5, 37, 52–55]. As a consequence, ventilator associated morbidity and mortality is reduced [45, 52–55].

Spinal anesthesia was reintroduced into pediatric anesthetic in the mid-1980s in an effort to reduce the respiratory complications, especially apnea, after surgery in preterm and ex-preterm infants. The impact on the outcomes from anesthesia was significant [6, 38, 56, 57]. As a result, spinal anesthesia and, more recently, caudal analgesia have been advocated for high-risk neonates at risk for perioperative apnea after surgery [1, 3, 7, 9, 56, 57]. A recent Cochrane review that investigated the perioperative risk of apnea in infants anesthetized with spinal or general anesthesia (sevoflurane, desflurane) demonstrated that the incidence of postoperative apnea after spinal anesthesia for inguinal hernia surgery in preterm infants is reduced by 47% and in infants without a history of apnea by 66% compared with that after general anesthesia [56–58]. Overall, oxygen saturation, bradycardia, and the need for respiratory support and analgesics were similar for spinal and general anesthesia. A recent systematic review of spinal versus general anesthesia in premature infants undergoing inguinal hernia repair reported significantly fewer episodes of apnea and bradycardia and the need for mechanical ventilation in the spinal group compared with general anesthesia [57]. However, there were no differences in the postoperative oxygen requirements, frequencies of prolonged apnea and oxygen desaturation <80%, and hospital stay. Distinguishing these two anesthetic techniques has been hampered by a paucity of studies and their poor study design.

Ex-premature infants today differ from those from the 1980s. Improved neonatal intensive care, ventilation strategies, and surfactant have reduced the incidence and severity of bronchopulmonary dysplasia.

Regional anesthesia may have salutary effects on gastrointestinal function. It enhances the early return of gastrointestinal motility [48, 59, 60], particularly after gastroschisis repair [23, 35, 47]. In necrotizing enterocolitis, the vasodilatory effects of autonomic blockade may improve splanchnic perfusion [35, 59], whereas opioids increase intestinal smooth muscle tone that may increase the risk of anastomotic leaks [59]. Lastly, oral feeding may resume earlier, and the speed of recovery after minor surgery reduced after a regional block [6, 37, 56].

The immunosuppressive effect of regional anesthesia is attenuated compared with that reported with opioids [23, 24, 60]. Local anesthetics, but not opioids, stimulate natural killer cells, which play an important role in nonspecific cellular mediated and antitumor immunity [25, 60]. Local anesthetics (e.g., bupivacaine) also confer antimicrobial action and inhibit bacterial growth [60].

Finally, regional anesthesia also confers economic benefits that include reducing the anesthetic costs, reducing the number of days in the neonatal intensive care, and facilitating earlier discharge and more efficient use of the ward nurse's time. However, to realize these benefits, the staff must be trained to care for neonates with epidural infusions and other regional blocks.

Risks: Although the efficacy of regional anesthesia is not disputed, opinions remain divided on our ability to safely perform regional anesthesia in neonates [34, 61]. Some consider the risks of regional anesthesia in this age group too great for routine use by individuals who do not have the requisite expertise [34, 48]. Even though the risks associated with opioid and epidural analgesia in children are similar [61, 62], the risks associated with epidural analgesia and peripheral nerve blocks in neonates are small [7, 61]. The numbers of neonates in published surveys of regional anesthesia are relatively small when compared with the numbers of children and adults who were given the same anesthetics [38, 62–77]. The aggregate of published series from approximately 102 institutions yielded only 1 serious complication, meningitis, in the 2811 published cases (Table 16.1). Serious complications, as rare as they are, usually occur early "at the end of the needle," i.e., when the anesthesiologist is still present. For example, the risk of a dural puncture is approximately 1:255, and convulsions 1:1405 in neonates (Table 16.1). Every effort should be incorporated in the anesthetic plan to eliminate drug errors, a feature in the UK audit [63]. Anecdotal reports of spinal cord injuries bear testimony that these unfortunate disasters can occur [78]. In general, we recommend that neonatal epidurals should only be performed by those with the technical expertise to place these blocks, despite the advent of ultrasound that may reduce the risks and with the safeguards to select the correct drug and dose [7, 79].

Anatomical Considerations [80–87] (Table 16.2)

Ultrasound and anatomical studies have demonstrated that the conus medullaris (the terminal end of the spinal cord) lies between L1 (first lumbar vertebrae) and L2 in the majority of neonates including preterm infants [17, 82–84]. The conus is not fixed but moves with changes in body position [86], although rarely does it extend caudad to L3. A conus that extends below L3 suggests the presence of a tethered cord [17, 82–87]. The dural sac usually terminates between S2 and S4 but may lie within millimeters of the sacral hiatus [17, 84, 87].

The shape of the vertebral column develops over the first year of postnatal life. At birth, the vertebral column has a single shallow anteriorly concave curve extending from the C1 (first cervical vertebrae) to L5. A secondary cervical curve appears when head control is achieved, usually by 6 months, and the lumbar curve develops with weight bearing by ~1 year. In neonates, the spinous processes are parallel and horizontal facilitating a midline approach to the epidural space at all levels. The largest intervertebral spaces are found between T12 and L1 (12th thoracic vertebrae) and L5 and S1 (first sacral vertebrae), respectively.

Table 16.2 Important anatomical and physiological similarities and differences between neonate and adolescents (adults)

Anatomy	Neonate	Adolescents (adult)
Conus medullaris	L1–L2	L1
Dural sac	S2–S4	S2–S4
Intercristal line	L4	L4
Vertebral column	Concave C1–L5	Secondary curves
	Main cartilaginous	Ossified
Spinous processes	Lumbar more horizontal, parallel Orientation T10–T12 similar to lumbar Midline approach easy	Lumbar angled caudad All thoracic spines angled caudad
Intervertebral space	Largest T12–L1; L5–S1	
Ligamentum flavum	Thinner, less dense	Thicker, fibrous
Epidural space	1–2 mm; less compliant spongy gelatinous fat lobules	Compliant Densely packed lobules fibrous strands
Sacrum	Flatter; less ossified	Fully ossified by 30y
Nerves	Thinner less myelination	
CSF volume	4 mL/kg	2 mL/kg
Physiology		
Blood pressure	Stable	Hypotension
Pulse rate	Stable	Bradycardia
Respiratory	Diaphragmatic function improved, ventilatory response CO_2 enhanced	Similar
CNS	Cortical arousal reduced Lower BIS	Similar
Endocrine	Inhibition stress response	Similar
GIT function	Earlier return	Similar

The sacrum is narrower and flatter, ossification is incomplete, and the vertebrae are separate facilitating sacral intervertebral epidural blocks. Sacral dimples or pits may reflect an occult spina bifida, which should be excluded using ultrasound, CT, or MRI before attempting a neuraxial block.

A posterior midline approach to the epidural space in neonates is regarded as the safest approach for several reasons. With a triangular spinal canal, the widest aspect of the epidural space is the midline where the epidural veins and arteries are less dense [87]. The epidural space is narrow (0.9–2.4 mm; median 1.5 mm) [17, 88, 89] and less compliant, whereas the ligamentum flavum is thinner and less dense and offers less resistance to the advancing epidural needle than in adults. Pressures generated during the passage of an epidural needle through the ligamentum flavum range from 35 to 105 mmHg (mean 70 mm), and the epidural pressures range from 1 to 10 mm Hg [88].

The epidural fat consists of spongy gelatinous lobules with distinct spaces and offers minimal resistance to the passage of local anesthetic or an epidural catheter [5]. The epidural veins have no valves and connect directly with intracranial veins. As a consequence, air or drugs inadvertently injected into the epidural veins can easily reach the brain without impediment.

The effective concentration of local anesthetics in neonates is less than in older children as the nerves are thinner and less myelinated. The nerve trunks to the lower extremities do not reach full myelination until the second year of life. The degree of myelination influences the pharmacodynamic effects of local anesthetics.

The CSF volume in neonates <1.5 kg is 4 mL kg^{-1}, relatively large compared with adults and older children, 2 mL kg^{-1}. CSF production in neonates, 0.35 mL min^{-1}, is greater than in adults. This explains in part why neonates require proportionately larger doses of local anesthetic for spinal block than in older children.

In terms of peripheral nerve blocks, it is important to appreciate that the muscle layers of the thoracic and abdominal wall are thinner, less well defined, and more compliant in neonates than in older children. The sciatic nerve divides within the popliteal fossa [90], the ilioinguinal and iliohypogastric nerves lie 3–5 mm medial to the anterior superior iliac spine [91], and the musculocutaneous nerve is easily included in an axillary block because of its proximity to the divisions [92] (Fig. 16.1).

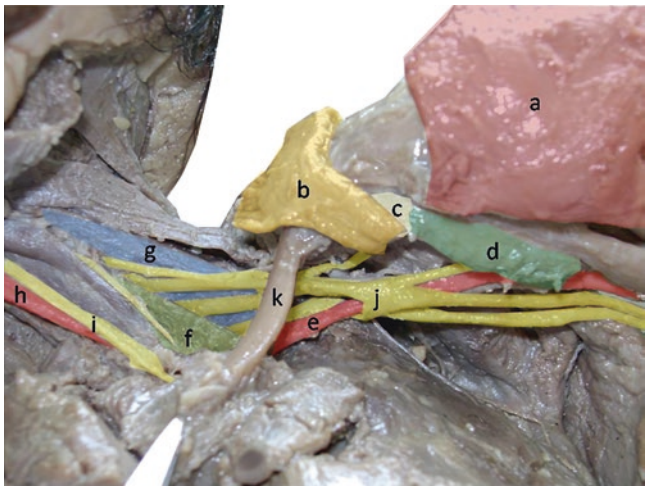

Fig. 16.1 Anatomical dissection of the axilla in a neonatal cadaver demonstrates the brachial plexus (**j**) and related structures within the axilla and at the root of the neck. Note the close relationship between the axillary artery and the cords and branches of the brachial plexus. The musculocutaneous branch is easily included even with small volumes of local anesthetic. Structures identified include the (**a**) pectoralis major and (**b**) pectoralis minor muscles, (**c**) coracoid process, (**d**) coracobrachialis muscle, (**e**) axillary artery, (**f**) anterior and (**g**) middle scalene muscles, (**h**) common carotid artery, (**i**) vagus nerve, and (**k**) clavicle

Pharmacological Differences

The pharmacological differences in neonates vary with gestational age-related changes in body fluid compartments, plasma protein levels, distribution of cardiac output, and the functional maturity of the liver and kidneys [93]. Other contributing factors include less body fat (15% body weight) and skeletal mass (25% body weight), a proportionally larger brain and liver, and greater cardiac output and regional blood flow to vessel-rich organs resulting in more rapid uptake of drugs.

Neonates are at greater risk for intravenous drug toxicity than older children [2, 93–98]. With smaller concentrations of albumen and α_1 acid glycoprotein [76, 94–100], the free fraction of circulating intravenous drugs in neonates is increased [101, 102]. Plasma concentrations of α_1 acid glycoprotein, an acute phase protein, increase in acute illness and after surgical stress [76, 96]. This difference protects against a local anesthetic overdose by attenuating the free fraction of the local anesthetic, particularly the amides. Furthermore, a greater fraction of local anesthetic is excreted unchanged in the urine because of the reduced hepatic blood flow and immature cytochrome P450 (CYP) enzyme system [76, 96]. The plasma cholinesterase activity in neonates is 50% that in young children and adults, which may delay the clearance of ester local anesthetics such as chloroprocaine [103, 104]. However, on balance, chloroprocaine is viewed as a safer local anesthetic than the amide anesthetics in neonates because it is very rapidly metabolized by the ubiquitous enzyme, pseudocholinesterase, even if administered inadvertently intravascularly [2, 38, 105–108].

Vascularity of the injection site and regional blood flow influence the rate of uptake of local anesthetics. The rate of absorption and therefore the peak serum concentration is reduced by vasoconstrictors. Epinephrine prolongs the duration of action of local anesthetics [109–111] by up to 50% in neonates [6, 110–112]. In the author's experience, the duration of caudal bupivacaine is virtually doubled by the addition of epinephrine 1:400,000 (unpublished data). However, during continuous epidural infusions of lidocaine with or without epinephrine, the blood concentration of lidocaine within the first hour is reduced in the presence of epinephrine, whereas after 2 h, the blood concentrations of lidocaine are similar [109]. Hence, epinephrine is recommended for single-shot caudal epidural blocks but not for continuous infusions of lidocaine.

Lung function also plays an important role in modulating the duration of action of local anesthetics. Approximately 60–80% of an intravenous lidocaine bolus is absorbed on the first pass through the lungs. However, in neonates with right to left intracardiac shunts, the reduced uptake by the lungs may increase the peak blood concentration by up to 100%, increasing the risk of local anesthetic toxicity [113].

Little is known about the pharmacokinetics of longer-acting local anesthetic agents in neonates [2, 75, 76, 94, 95, 99]. Guidelines for epidural infusions of bupivacaine in neonates and infants <6 months of age based on anecdotal reports of toxicity recommend 0.2 $mg.kg^{-1}\ h^{-1}$ bupivacaine or ropivacaine and in infants >6 months of age recommend up to 0.4 $mg.kg^{-1}\ h^{-1}$. The blood concentrations recorded in neonates were greater than in infants, although the concentrations in both groups were <2–3 $mcg.mL^{-1}$, i.e., well below the threshold for toxicity in humans [75, 76, 99]. Plasma concentrations of bound bupivacaine accumulate after a 48-h infusion [75], whereas concentrations of bound ropivacaine are independent of the duration of infusion up to 72 h [76]. Thus, ropivacaine appears to be the safer local anesthetic for epidural infusions 48–72 h in duration in neonates [76, 99].

Neuraxial Blockade

Spinal

Bainbridge described the first spinal anesthetic on an infant in 1899, and early in the twentieth century, Lord H Tyrell Gray suggested that spinal anesthesia "would occupy an important place in the surgery of children in the future." Although the popularity of spinal anesthesia waned as the safety of general anesthesia improved, these prophetic words

may still be realized considering the current controversy regarding the neurotoxicity of general anesthetics in neonates. The popularity of spinal anesthesia was rekindled in the early 1980s when Abaijan proposed its use for ex-premature infants undergoing inguinal hernia repair. Currently, spinal anesthesia remains limited to selected high-risk infants in whom general anesthesia may pose a major risk [114].

Spinal anesthesia has been used alone or in combination with an epidural for a wide variety of surgeries including inguinal hernia repair, ligation of patent ductus arteriosus, pyloromyotomy [42, 49], gastrostomy, gastroschisis [115], omphalocele, exploratory laparotomy, lower abdominal surgery (colostomy, anoplasty, rectal biopsy, circumcision) meningomyelocele repair, or orthopedic surgery [6, 116].

Spinal anesthesia has a much shorter duration of action in neonates than in adults despite the relatively larger doses used in the former. The duration of action appears to be directly correlated with age [112, 117, 118]. For practical purposes, an effective plane of surgical anesthesia after spinal block lasts ~40–60 min with bupivacaine, levobupivacaine [119, 120], and ropivacaine [120, 121], up to 1.5 h with tetracaine plain or 2 h with tetracaine with epinephrine [6, 112], and up to 1 h after lidocaine 3 $mg.kg^{-1}$ with epinephrine [112].

Spinal anesthesia has been used to facilitate placement of an epidural block [11] in order to prolong the duration [11, 12]. Intrathecal clonidine (1 $\mu g.kg^{-1}$) may also be used to perform surgery, although it is associated with more sedation and apnea than the local anesthetics alone [117].

Spinal anesthesia rarely produces significant changes in heart rate or blood pressure in neonates, even with blockade to thoracic levels and in infants with congenital heart disease [7, 48, 122–124]. Reduced cortical arousal caused by peripheral deafferentation [41, 125] or a decrease in cerebral blood flow [126] should be considered when concomitant sedatives are administered [125]. Furthermore, a single dose of sedation (ketamine 1–2 $mg.kg^{-1}$, midazolam 0.2 $mg.kg^{-1}$, or propofol 1 $mg.kg^{-1}$) increases the risk of perioperative apnea [6, 116, 127].

Complications: The incidence of serious complications (nerve injury, meningitis, arachnoiditis) [128, 129] after spinal anesthesia, based on two large series, is small [6, 116]. Failure rates for effective spinal anesthesia in neonates range from 5–10% (in experienced hands) [6, 130] to 17% (trainees) [5, 28] with a bloody tap rate of 10% [116]. Failure was associated with bloody taps in the GAS study [130]. Bradycardia (<100 bpm) and apnea can be treated with tactile stimulation, atropine 0.1 $mg.kg^{-1}$, or ventilatory support as indicated. The incidence of bradycardia ranges from 1.2 to 1.8% [6, 116]. A high spinal (0.1–0.6%), heralded by apnea but uncommonly associated with hypotension or bradycardia, has been associated with large doses of local anesthetic, early leg raising (e.g., when placing the electrocautery pad), or "top-ups" when the dermatome level is inadequate. Unilateral spinal blockade in neonates has also been described [131]. Plasma concentrations of local anesthetics after spinal anesthesia are small (0.2–0.3mcg/mL) and unaffected by the addition of epinephrine [132].

Technique: Using a sterile technique, a spinal anesthetic is placed using a 25ga or styleted 22ga 1.5inch (3.8 cm) spinal needle in the sitting or lateral decubitus position. Currently, chlorhexidine in 70% alcohol is the recommended skin preparation. The usual puncture sites are L3–L4 or L4–L5. A prior ultrasound scan is useful but not required, to determine the exact location of the dural sac and to exclude any central nervous system or bony anomalies. Once free flow of CSF is obtained, the local anesthetic can be administered using a 1 mL syringe. The onset of the block is heralded by profound motor block in the lower extremities within seconds of completion of the spinal. Care should be taken to avoid positioning the infant head-down, i.e., when placing the electrocautery pad on the back, before the block height is set to avoid a high spinal block. Instead, the child should be log-rolled to apply monitors, cautery pads, and other devices.

Gentle stroking, soothing, or dextrose water on a pacifier calms most neonates. Intravenous sedation may be necessary in ~25% of cases [6, 116, 130] but may be associated with apnea [9, 116].

Dose guidelines:
Hyperbaric tetracaine 0.5% 0.6–1 $mg.kg^{-1}$.
Isobaric bupivacaine or ropivacaine 0.5% 0.1 $mg.kg^{-1}$.
Hyperbaric bupivacaine 0.75% 0.1mL.kg^{-1}.
Hyperbaric lidocaine 3 $mg.kg^{-1}$.

Adjuvants:
Epinephrine 5–10 $mcg.kg^{-1}$ to prolong the duration of action
Clonidine 1 $mcg.kg^{-1}$ to prolong analgesia [118].

Caudal Block

Caudal analgesia is frequently used to provide analgesia for surgery below the umbilicus [7, 43, 81, 133]. The popularity of caudal blockade stems from its simplicity, safety, and efficacy, but more importantly, that additional local anesthetic can be administered if the anesthetic begins to wane before the procedure is completed. This block is usually combined with general anesthesia [7]. Larger doses of local anesthetics are required for upper abdominal surgery [134], although achieving this level of block is less predictable unless a caudal catheter is introduced. Caudal blocks are effective as the sole anesthetic, particularly for ex-premature infants undergoing inguinal hernia repair, thereby preventing periopera-

tive apneas. They have also been used to reduce incarcerated inguinal hernia [44], to improve compromised perfusion after umbilical catheterization [135] and penile block [136], or to facilitate PICC line placement in extreme preterm infants [137].

Anatomy: The sacral hiatus lies between the sacral cornu, two prominences that represent the remnants of the fifth sacral arch, and extends to the fused arch of the fourth sacral vertebra. The sacrococcygeal membrane, an extension of the ligamentum flavum, covers the sacral hiatus separating the caudal space from the subcutaneous tissue. Considerable variation in sacral hiatal anatomy exists mainly due to incomplete posterior fusion of other sacral vertebrae. However, a few important surface landmarks can be used to enhance success in both normal and abnormal sacra. The sacral hiatus virtually always lies at the apex of an equilateral triangle which has the line drawn between the posterior superior iliac spines as its base (Fig. 16.2). The intersection of a line drawn from the patella through the greater trochanter (with the hips flexed at 90 degrees) to meet a line drawn down the vertebral column is another useful landmark (Fig. 16.3).

Technique: Caudal block can be performed in the lateral decubitus position or prone knee chest position—a useful position for an "awake" caudal block [138] (Fig. 16.3). Under sterile conditions, a short bevelled needle, held between the thumb and index finger, is introduced at approximately 30–45° to the skin and advanced until it pierces the sacrococcygeal ligament [139]. Some advocate up to 90° to skin [140] – this has become this author's preferred approach! A "give" can be felt as it enters the caudal space and can be confirmed by loss of resistance. Penetration of the sacrococcygeal membrane just above the sacral cornua carries a smaller incidence of bloody tap in the author's experience. The dural sac lies within 5–10 mm of the sacral hiatus in the majority of neonates [17], and thus changing the angle and advancing the needle, as described in adults, are unnecessary as it may result in a dural puncture or bloody tap [43]. Using a 22 g IV cannula is another popular approach [43, 141], but in the author's experience, it carries a greater incidence of failure (subcutaneous injection) and bloody taps in untrained hands.

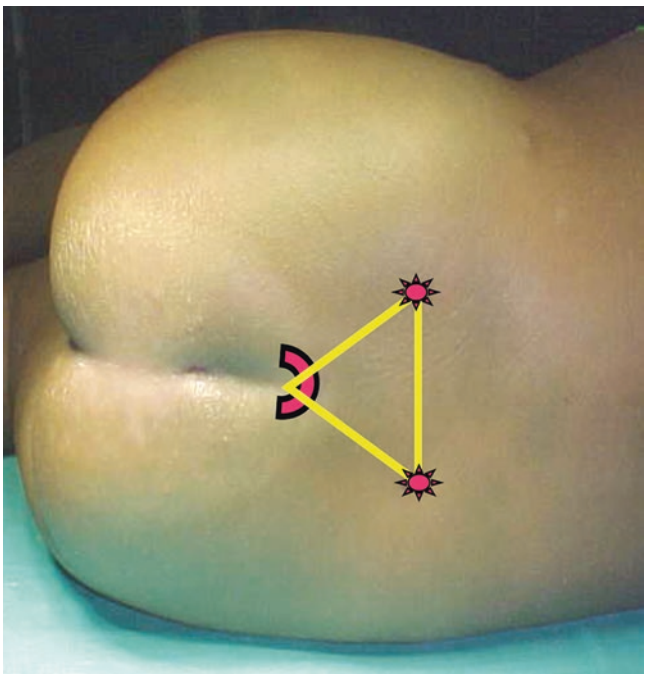

Fig. 16.2 Caudal block. The sacral hiatus lies at the apex of an equilateral triangle with the line drawn between the posterior superior iliac spines as the base

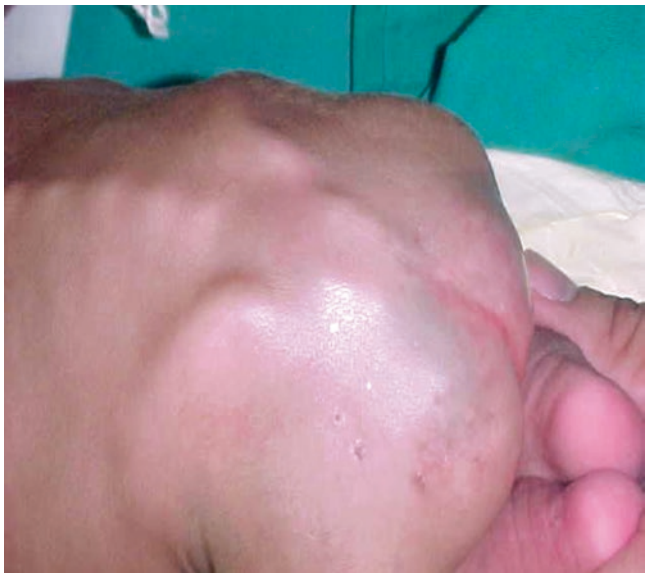

Fig. 16.3 Caudal block. The knee chest position may be used to facilitate placement of the caudal in awake neonates

Aspiration should be gentle since strong negative pressure may cause the low-pressure epidural vessels to collapse before a positive aspiration test can be elicited [43].

[Editor's Note. Our practice includes only IV catheters to achieve several purposes. First, once the needle tip punctures the sacrococcygeal ligament and advances 1–2 mm, only the catheter is advanced into the caudal space. If the needle has punctured the thin bony table of the sacrum, the catheter will accordion rather than advance smoothly confirming immediately that the needle/catheter is not in the caudal canal. Second, limiting the needle tip to traversing only the sacrococcygeal ligament reduces the risk of an intravascular or subarachnoid puncture. Third, we remove the needle leaving the catheter in place and observe for passive blood or CSF backflow. We do not aspirate the catheter at this time because the vein will collapse due to the negative pressure leading to a false-negative detection of an intravascular cannulation.]

After negative aspiration for blood and CSF, the required volume of local anesthetic can be injected [Editor's Note. We

recommend that the entire volume of local anesthetic that will be administered be treated as a test dose, injecting 10–15% of the predetermined volume at a time while palpating the soft tissues just cephalad to the sacral hiatus to detect swelling from a subcutaneous injection and watching the ECG for conformational changes described above.] In the event of a "bloody tap," the needle should be redirected or removed and reinserted more cephalad. Local anesthetic injection should proceed with caution after a bloody tap considering the greater risk of an intravascular injection under these circumstances [142]. Ultrasound can be used to "visualize" the spread of local anesthetic within the caudal epidural space [143].

Complications: Dural puncture and subsequent injection may lead to a total spinal and respiratory arrest (apnea). Systemic toxicity after accidental intravascular or sacral intraosseous injection may be heralded by ECG changes (ST segment elevation, peaked T waves or arrhythmia) from injection of epinephrine, cardiovascular collapse, or convulsions. Intrapelvic injections [144, 145] are avoided with the correct technique. Urinary retention does not occur when only local anesthetics are used [146]; urinary retention is, however, associated with coadministration of opioids [147]. Nerve injury and neurological deficits have not been reported in neonates. Historically, inclusion dermoid tumors have been reported but only anecdotally [148, 149]. The risk of introducing nucleated epidermal cells from stratum spinosum during caudal block is extremely small and is similar with 22 g hollow needles and styleted 22 g caudal block needles [148, 149].

One peculiar complication associated with caudal blocks in infants undergoing hypospadias repair is a postoperative ureterocutaneous fistula, a finding that occurred more commonly than after a penile block, was recently reported [150]. The accompanying editorial elegantly articulated the flaws in this retrospective review [151]. Despite reports of an association in a systematic review which acknowledged publication bias [152], recent evidence has focused on the surgery as the cause and dispelled an association between caudal analgesia and urocutaneous fistulae [153, 154].

Dosage: Many formulae have been proposed for caudal block based on the neonate's weight, age, and length with insufficient consideration to the increased free fraction of drug due to reduced protein binding, especially in the case of bupivacaine [101, 102, 133, 142, 155–158]. The most practical is that suggested by Armitage [142]:

0.5 $mL.kg^{-1}$ of local anesthetic for sacro-lumbar dermatomes.
1.0 $mL.kg^{-1}$ for lumbar thoracic dermatomes (sub-umbilical).
1.25 $mL.kg^{-1}$ for mid-thoracic dermatomes (upper abdominal).

Bupivacaine 0.125–0.25% [159, 160], ropivacaine 0.1–0.2% [161–164], levobupivacaine 0.25% [165], chloroprocaine 3% [38, 105–107], or lidocaine 1% with 1:200,000 epinephrine has been effective as a single dose. The duration of analgesia depends upon the dose (concentration and volume) and specific local anesthetic administered, the use of epinephrine, the site of surgery, and whether a continuous catheter is used [38, 81]. Increasing the concentration of local anesthetic does not offer additional advantage compared with standard concentrations but may increase the incidence of side effects and/or complications and reduces the volume that may be administered, which itself may limit the height the block achieves. Despite numerous publications that provide guidelines for the optimal dose and volume of bupivacaine (or equivalents of other local anesthetics) for caudal analgesia in infants <1 year of age, a review of more than 14,000 infants in the pediatric regional anesthesia network documented large variability in the dose and volume used [166]. Clonidine has been added to prolong the duration of analgesia but is associated with an increased risk of sedation and apnea [167, 168].

Caudal Catheter Techniques

An epidural catheter can be introduced via an IV catheter in the sacral hiatus to prolong the duration of the caudal block [12, 38] or to access the sacral, lumbar, or thoracic epidural space for a block at a more cephalad level [5, 73, 169–181]. Specialized equipment is not required to perform this block [4]. This technique was developed before the introduction of pediatric epidural needles. The risk of dural puncture or spinal cord injury may be less than with direct lumbar or thoracic epidural placement in less experienced hands [5, 18].

A caudal block of "intermediate" duration (for a surgery of prolonged duration and for a brief period postoperatively) may be achieved by administering supplemental doses of local anesthetics (ropivacaine, lidocaine, or chloroprocaine) through a caudal IV catheter with a 5 cm or longer Luer lock IV extension or through an epidural catheter threaded caudally. The catheter and extension should be padded to prevent kinking the tubing and secured with a Tegaderm and/or tape. At the end of the surgery or in PACU, a final dose of local anesthetic may be administered before the catheter is removed. [Editor's Note. In our experience, some IV catheters are flimsy and prone to kinking if left in the sacral hiatus for 1 or more hours. We have had mixed success administering a top-up dose of local anesthetic through a 22 ga IV catheter at the end of surgery because the lumen was occluded (possibly kinked). If a top-up is essential in such a case, either an epidural catheter should be inserted in the first place or the IV catheter

must be removed and a new IV cannula is inserted through the sacrococcygeal ligament.]

Technique: An 18 or 20G IV cannula, Crawford needle, or purpose designed kits [18, 170] can be used to access the caudal space in order to site an indwelling catheter. A 19–24G epidural catheter that passes easily through the cannula is measured along the neonate's back from the sacrococcygeal puncture site to the level of the planned surgical incision. The catheter can then be introduced gently into the caudal/epidural space to this predetermined length (Fig. 16.4). It is important to avoid applying force to the catheter should resistance be encountered while threading it as the catheter tip may impinge on a nerve root or exit through a foramen, puncture a blood vessel or dura, or form a loop or knot in the catheter.

Flexion or extension of the infant's spine [5, 54], flushing the catheter with saline [5, 169], or twisting/rolling the catheter between the operator's fingers [5, 54] can be used to further advance the catheter. It is important to position the tip of the multi-orifice (closed tip) catheter at the most cephalad dermatome level to achieve an adequate block as only the proximal orifice is perfused at the usual (small) epidural infusion rates (although local anesthetic boluses delivered manually perfuse all three orifices) [182]. Even if the catheter is threaded to the "optimal level" for effectiveness, a recent study suggested that catheters can migrate one to two vertebral levels and that the level of the tip should be verified if the catheter is left in situ postoperatively in neonates and infants [183]. [Editor's Note. We use 19 ga epidural catheters, do not verify the level of the tip, and have had complete success with analgesia up to 3 days in neonates, infants, and children without verification.] Nonetheless, smaller gauge (24G) flexible catheters are more likely curl in the sacrolumbar epidural space and fail to reach their target dermatome level compared with larger diameter catheters [184]. This problem can be overcome by using styleted catheters, which are expensive [174, 176, 177].

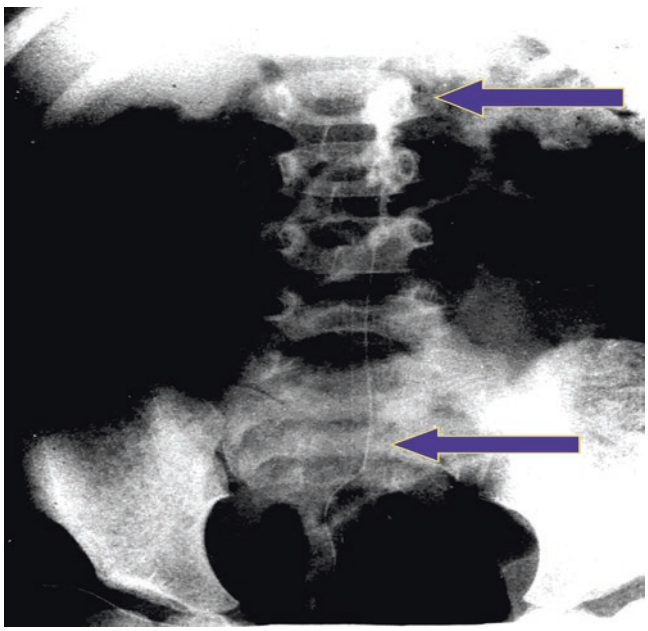

Fig. 16.4 A predetermined length of catheter can be inserted via the sacral hiatus and threaded up the epidural canal to reach the desired dermatome level. An epidurogram or ultrasound can be used to confirm the position of the tip of the catheter. Here, an epidurogram demonstrates contrast in the epidural space at the L1 level (upper arrow) at the tip of the catheter. In addition, the contrast filled caudal catheter introduced at the sacral hiatus (lower arrow) can be followed up in the spine to the level of the tip at L1 (arrows)

We prefer to use larger volumes of local anesthetic in neonates rather than force catheters to reach the target dermatome level within the epidural space, although this is a trade-off between the degree of dilution of the local anesthetic and the maximum volume that could be administered to preclude toxic blood concentrations during a continuous infusion.

The preferred method used to confirm the dermatome level of the tip of epidural catheters varies. Techniques used to identify the location of the tip include epidurography [5, 73, 171, 185], fluoroscopy, electrocardiography [177, 186], nerve stimulation [180, 181], and ultrasonography [143, 172, 178, 187]. In contrast, some practitioners do not verify the position of the catheter tip after inserting a predetermined length of catheter to reach the desired dermatome level but depend on the effectiveness of the epidural block to confirm a satisfactory catheter position.

Recently, two studies shed light on catheter tip migration in neonates and infants. When the final position of the catheter tip verified with ultrasound was compared with landmark based measurements to reach the desired dermatome level (lumbar and thoracic levels) in neonates and infants, ultrasound documented the catheter tip 4.2 cm more cephalad than that based on blindly passing the predetermined length of catheter [187]. In a study of caudally passed thoracic radio-opaque catheters, fluoroscopy and epidurograms demonstrated that almost two-thirds of the catheter tips were either caudad or cephalad ≥1 vertebral levels and 27% of the catheter tips reached T4 level [183]. Of particular concern was that catheter tip migration ≥2 vertebral levels occurred *only* in infants <6 kg in weight and <73 days of age. These data emphasize the need to document the level of the catheter tip in neonates. Electrical stimulation with wired catheters allows real-time adjustment of the catheter level but requires specifically designed equipment [167]. In the author's experience, a 20 g nylon catheter (Portex®) passed through the epidural space to within one vertebral body of the intended dermatome level achieved the desired level of analgesia in more than 500 neonates. Difficulties have been described when threading the catheter in premature infants and when using a Tuohy needle [12, 73]. The curve of a Tuohy needle

may cause the catheter to curl if the lumen is not properly aligned within the long axis of the caudal canal.

Complications: Complications include failure to position the catheter at the desired level, dural puncture, intravascular placement [54, 175], catheter colonization (30%) [188, 189], and one reported case of meningitis [54]. Careful aseptic technique with chlorhexidine, rather than povidine-iodine, for all catheter techniques carries a smaller risk of colonization [190]. Tunneling the catheter subcutaneously, away from the anal region, may further reduce the risk of colonization [189, 191] especially for prolonged infusions [188]. However, it is crucial to appreciate that colonization does not progress to infection or abscess formation in the nervous system; epidural abscesses depend on hematogenous spread and seeding of bacteria (most often *Staphylococcus aureus*) or fungus [192].

Dosage: Commonly used local anesthetic doses include 0.5–1.0 mL kg^{-1} 0.175–0.25% bupivacaine, 0.15–0.2% ropivacaine, or 1.5–3% chloroprocaine loading dose; the volume of each solution depends on the number of dermatomes required to be covered [5]. Continuous infusion rates at 0.3 mL/kg/h maintains the height of an established block. In the case of bupivacaine, the concentration of the infusion fluid must be restricted to preclude toxic plasma concentrations in neonates beyond 24 h: 0.1% concentration is usual at a volumetric infusion rate of 0.2–0.25 mL/kg/h [193]. This has proven to be an issue with bupivacaine in neonates who appeared jittery as a result of an increased free fraction in this age group [102]. In the case of 0.2% ropivacaine, toxic plasma concentration is not achieved with these doses after 48–72 h of infusion [76]. [Editor's Note. We infuse 1.5%–3% 2-chloroprocaine (1 mL/kg) as an epidural solution in awake neonates for lower abdominal superficial surgery as it is the least toxic of the local anesthetics. Subsequent infusion rates are 0.5–1.5 mL/kg/h [38]].

Lumbar and Thoracic Epidural

Lumbar epidurals are most effective for lower abdominal, pelvic, and lower limb surgery, whereas thoracic epidurals are effective for upper abdominal or thoracic surgery [189], particularly in high-risk patients with respiratory disabilities [194]. Experience with these epidural techniques in neonates is limited [4, 7, 35, 54, 55, 63, 76, 77].

Few dermatomes are involved in the transverse abdominal incision favored by pediatric surgeons and thus can be easily covered by an accurately placed epidural. Most epidural blocks are performed after the neonate/infant has been anesthetized, although if general anesthesia is to be avoided, it can also be performed with sedation [10] or after initial spinal blockade when indicated [11]. In view of the potential risk of spinal cord trauma, thoracic epidurals should only be performed by experienced providers familiar with placing epidural blocks in neonates.

Technique: Using a sterile technique, the skin should be punctured with a needle to facilitate smooth insertion of a 19 or 20 g Tuohy needle. A midline approach is preferred since the epidural space is widest at this point and the epidural vessels less dense. The interspace chosen should be as close to the dermatome of the surgical incision as possible. The needle angulation is dependent on the level of epidural puncture and is greatest in mid-thoracic region. Below this level, a more perpendicular approach can be used since the spinous processes are almost horizontal when the back is flexed [194, 195] (Fig. 16.5). T12–L1 and L1–L2 interspaces are the largest and most easily palpable processes. The skin-epidural distance ranges from 5 to 12 mm depending on the gestational age and weight of the neonate [35]. The depth of the epidural space can be accurately measured using ultrasound [17].

Both air and saline have been advocated for the loss of resistance test to identify the epidural space [195, 196]. Saline is more popular according to recent survey [196], but air is perhaps more sensitive [35, 194]. A recent practice advisory has suggested that either air or saline could be used [197]. Both techniques have issues—saline dilutes the local anesthetic and air may embolize (and cause acute neurologic injury via the artery of Adamkiewicz) [198]. The volume of both saline and air that is used to identify the epidural space should be restricted to 0.5–1 mL. A "drip and tube" method has also been described [67].

A catheter should be introduced at least 2 cm into the epidural space for continuous infusion or intermittent "top-ups" depending on whether an open tip or closed tip catheter is

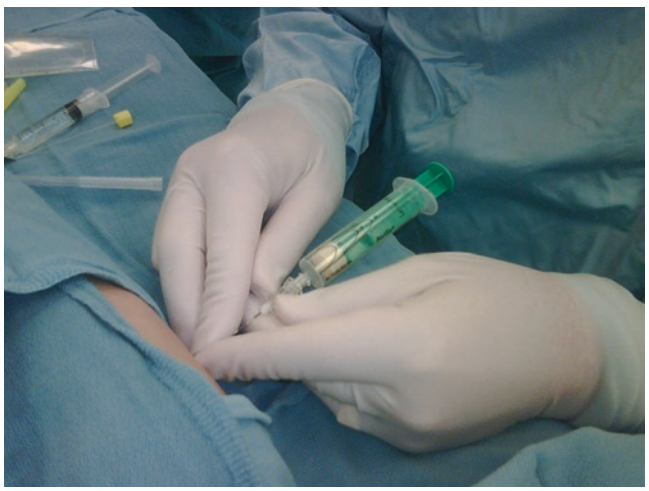

Fig. 16.5 The epidural needle can be introduced almost vertically to the skin in neonates when the back is flexed in the lateral decubitus position. Loss of resistance to air is considered more sensitive for detecting the 1–2-mm-wide epidural space

used [182]. This is best done after the "test dose" has "opened" the epidural space to facilitate the passage of the catheter [5, 169]. The length of catheter introduced is important. An excessive length of catheter runs the risk of unilateral blockade or vascular or subarachnoid puncture, whereas an insufficient length could result in a failed block or increased leakage of local anesthetic solution. Ultrasound can confirm the placement of the catheter as well as the location of the tip [178].

Complications: No serious complications, except dural puncture, have been reported in large published series [35, 54, 55, 63, 76, 77, 194, 199, 200] (Table 16.1). Anecdotal case reports of spinal cord injury and air embolus bear testimony to the potential for this disaster [201].

Dosing guidelines: An initial bolus dose of 0.5 mL/kg followed by an infusion of 0.1–0.3 mL/kg/h 0.15–0.2% ropivacaine or 0.1% bupivacaine provides satisfactory analgesia [35, 76]. A recent study suggested that 0.6 mL/kg is the optimal bolus dose for abdominal surgery [202]. A smaller initial bolus 0.33 mL kg^{-1} 0.25% bupivacaine or 0.2% ropivacaine is suggested for thoracic epidurals [203]. In the author's experience, larger volumes of up to 0.5 mL kg^{-1} may be required in small infants. *"Top-up"* doses should be half the original dose.

Sacral Epidural Block

Busoni described two approaches to the sacral epidural space [204, 205]. The *sacral intervertebral block* [206, 207] is possible in neonates since the sacral vertebrae are not fused. This block is particularly useful in neonates in whom the sacral hiatus cannot be identified and thus a caudal approach is not possible, e.g., obese neonates or high anorectal malformations with associated sacral abnormalities [207]. The *modified Taylor approach* [173, 204] between L5 and S1 is possible because of the large space between spinous process of the fifth lumbar vertebra and the rudimentary spinous process of the first sacral vertebra. These approaches are less risky for spinal cord injury or dural puncture [17, 87]. Furthermore, indwelling catheters for continuous infusions at these sites are less likely to become contaminated because of the greater distance from the anus than caudal catheters [204].

Technique: The posterior superior iliac spines are identified with the neonate in the lateral decubitus position with the hips flexed. A line between the posterior superior iliac spines bisects the second sacral vertebral arch (S2). The largest sacral intervertebral space (S2–S3) is easily identified 0.5–1.0 cm caudad to this line. The L5–S1 interspace is located 0.5–1.0 cm cephalad of this line and is also easily palpable provided the overlying sacral fat pad is thin. If difficult to palpate, an epidural needle can be introduced to contact bone and then "walked" off cephalad or caudad on the sacral vertebra till the interspace is identified.

After skin preparation, the skin should be punctured to facilitate insertion of the 19 or 20 g Tuohy needle. No flexion is required since the spinous processes of the sacrum are rudimentary. The epidural space can be identified using a "loss of resistance" technique. The Tuohy needle may be inclined to facilitate threading the catheter.

Dosing guidelines: These are the same as for caudal block.

Continuous Epidural Infusions

Postoperative analgesia can be maintained using intermittent "top-ups" [7, 35] or continuous infusions of local anesthetic [35, 63, 68–72, 75, 76, 99, 105–107]. As significant hypotension is unlikely, swings in blood pressure—a problem in adults—are not a feature in neonates. Intermittent "top-ups" are therefore a useful alternative when infusion pumps cannot deliver small hourly volumes of local anesthetic agents accurately.

There is no consensus on the optimal local anesthetic agent or concentration in clinical practice [7, 208, 209]. Dosing guidelines for racemic bupivacaine (i.e., 0.2 mg/kg/h for neonates and infants under 3 months) have proven to be safe and effective for both ropivacaine and levobupivacaine [7, 63, 75, 76, 99, 164, 193, 210]. No complications have been reported using this dosing guideline in more than 1400 neonates, infants, and children [193]. Similarly, no complications have been reported in neonates from both the PRAN data [7] and in over 500 neonates, ranging from 0.5 to 5 kg (author's unpublished experience).

Some have recommended a smaller loading dose of 0.5 mL kg^{-1} 0.25% bupivacaine followed 30 min later by a similar infusion dose of 0.08 mL kg^{-1} h^{-1} delivered by a volumetric infusion pump [211] (Table 16.3). For simplification, ease of calculation, and an adequate volume to ensure a complete block, an infusion of 0.1 mL kg^{-1} h^{-1} works well in neonates in the author's experience provided the catheter tip lies close to the dermatome of the surgical incision; others use dilute concentrations (0.1% bupivacaine or 1.5% chloroprocaine) at 0.2 mL/kg/h [Editor's Note]. Smaller infusion rates (0.06 mL kg^{-1} h^{-1}) have been advocated for thoracic epidurals [186] (Table 16.3). For neonates <2 kg, the author reduces the concentration of local anesthetic, to 0.1% ropivacaine or bupivacaine.

The editor uses primarily 2-chloroprocaine or lidocaine for all continuous epidural infusions in neonates for safety reasons. Once a particular infusion rate has been selected, regular assessment of the level of blockade, as well as an assessment of the degree of motor blockade, should be performed. Adjustments to the infusion rate should be made as

Table 16.3 Epidural infusions of bupivacaine and ropivacaine in neonates

Drug	Dose	Additive	Ages	Site	Author	Ref.
Bupiv	**0.2 mg/kg.h**		Neonate		Berde	[193]
Bupiv	**0.2 mg/kg.h**		Neonate, infant	L	Schenkman	[54]
Bupiv 0.2%	0.1 mL/kg/h		Neonate	L,T	Bosenberg	[35, 52]
Bupiv 0.2%	0.1 mL/kg/h		Neonate		Larsson	[75]
Bupiv 0.1%	0.2 mL/kg/h	F 1mcg/mL	Neonate, infant	L	Murrell	[36]
Bupiv 0.125%	0.2–0.3 mL/kg/h		Neonate, 4 m	L	Wolf	[257]
Bupiv 0.125–0.25%	0.25 mL/kg/h		Neonate, 6y	L,T	Luz	[102]
Bupiv 0.2%	0.2 mL/kg/h		Neonate, infant	L	Meunier	[101]
Ropivacaine 0.2%	0.1–0.2 mL/kg/h		Neonate, 1y	L,T	Bosenberg	[76]

L lumbar epidural, *T* thoracic epidural, *F* fentanyl
Note: Text highlighted in bold where the dose infused was described in mg/kg/h

necessary (Table 16.3). If the maximal infusion rate is reached and the child still remains agitated, a manual "top-up" dose of lidocaine may prove effective to increase the dermatome level of the block and establish whether the epidural block can be salvaged. If the block remains inadequate, then supplementation with a systemic opioid or epidural adjuvants should be considered. A check of the insertion site for signs of infection should also be included in the regular assessment.

Epidural Adjuvants

Few adjuvants have been used extensively in neonates despite the variety used in older children [212–214]. Most of these additives have been studied in inguinal surgery as the model to evaluate their efficacy and risk/benefit ratio. Whether these findings can be extrapolated to major abdominal or thoracic surgery is debatable. The potential risk seems unjustified for relatively minor surgery since oral or rectal analgesia with less risk appears equally effective.

Epidural fentanyl carries a significant dose-dependent risk of respiratory depression without substantial analgesic benefit [212]. Moreover, it causes urinary retention, pruritus, and ileus. Nausea, vomiting, and pruritus are difficult to assess in neonates and preterm infants but may be expressed as irritability, fussy, or "unsettled." When administered via a thoracic epidural, fentanyl is absorbed systemically and acts on the central nervous system. In the lumbar region, fentanyl probably acts locally as well as systemically.

Clonidine has been used as an adjuvant for caudal or epidural infusions in neonates. At the recommended bolus dose (0.5–1 mcg/kg) or infusion rate (<0.1 mcg/kg/h), the hemodynamic effects are mild. Clonidine provides synergistic analgesia and, unlike epidural opioids, produces little or no ileus, nausea and vomiting, itching, or urinary retention. Even at doses that cause sedation, the respiratory drive with clonidine is better preserved than with opioids.

Ultrasound Imaging of the Spinal Cord

Incomplete ossification of the posterior elements of the spinal canal in neonates allows accurate ultrasound evaluation of spinal cord structures with high frequency 7–12 MHz linear array transducer probes [83, 84, 178, 179, 215, 216]. The best acoustic views are obtained in preterm infants. Information about the anatomical relationships of the spinal cord, dura mater, and epidural space (size, depth) can be applied effectively [83, 84, 215, 216]. The skin-epidural depth can be measured and serve as a guide at which loss of resistance can be expected. The exact location of the conus can also be determined [86, 217].

In axial scans (Fig. 16.6a), the spinal cord is a hypoechoic (black) oval structure with a central hyperechoic (white) area representing the base of the paramedian sulcus. The hypoechoic spinal cord tapers to the conus medullaris. At this level, the rest of the vertebral canal is filled with multiple small rounded hyperechoic structures representing the cauda equina seen in cross section. The dura mater forms a hyperechoic (white) ring bordering the spinal canal; the pia mater is a hyperechoic ring surrounding the spinal cord. The cerebrospinal fluid is hypoechoic. The paraspinous muscles appear as an ovoid hypoechoic structure in either side of the midline.

In sagittal longitudinal scans (Fig. 16.6b), the spinal cord elements are bounded by the pia appearing as hyperechoic parallel lines that converge at the conus. The cord is homogeneously hypoechoic with a central hyperechoic line (central sulcus). The dura mater is the hyperechoic line closely applied to the bony elements. The spinous processes can be identified by the "saw tooth" effect at regular intervals above the spinal canal and its contents.

Using real-time imaging, ultrasound can verify the correct placement of a Tuohy needle, the injection of local anesthetic, and the position of the catheter within the epidural space [178, 215, 217]. The epidural space in neonates ranges from 1 to 3 mm in depth [17]. The orifice of a 19G (Portex®)

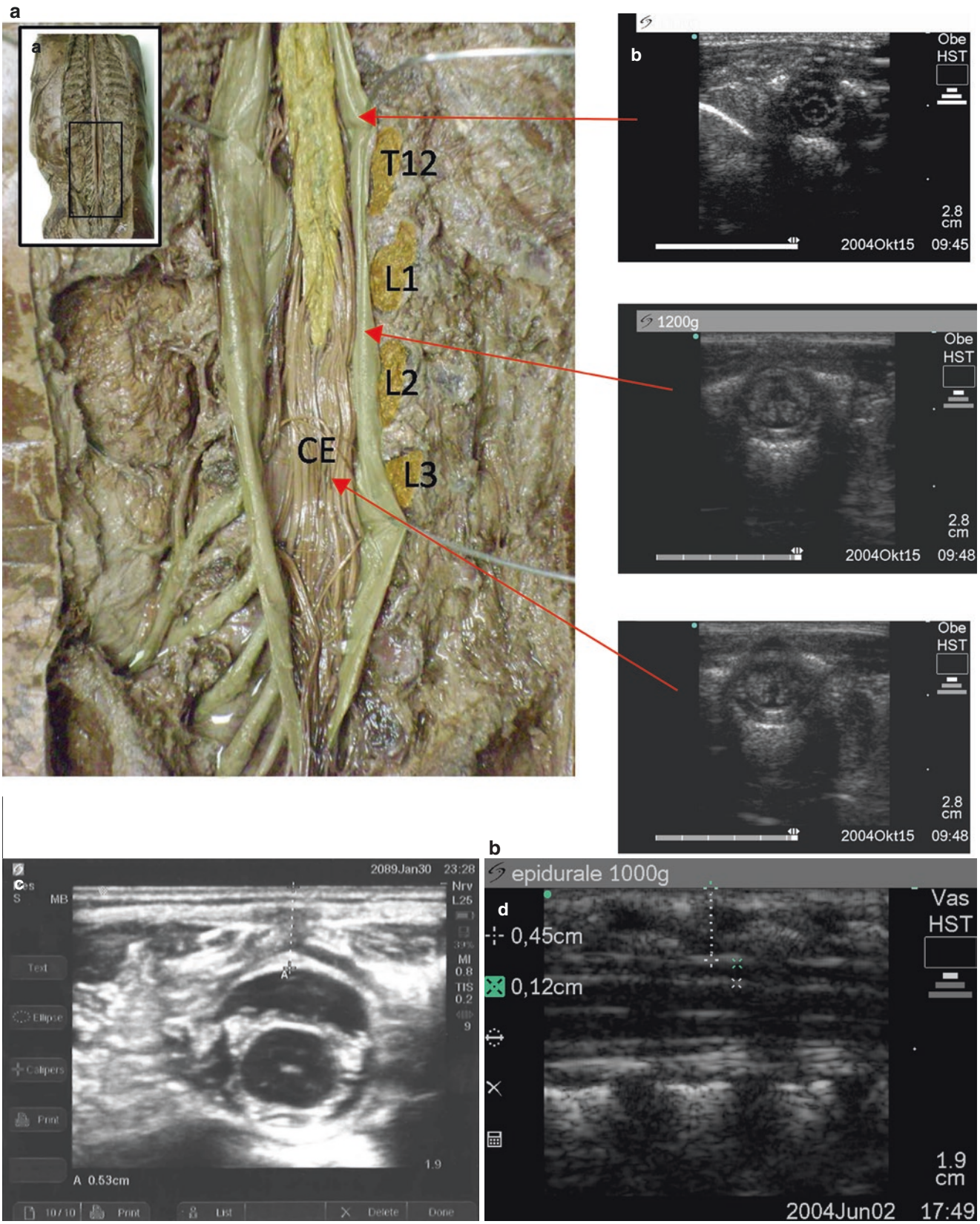

Fig. 16.6 Ultrasound image of the vertebral column (cross section—**a**; sagittal section—**b**). The depth the epidural space can be measured before placing the catheter. Abnormalities and normal variants of relevant anatomy can be excluded before placing an epidural block

or 20G (Arrow®) Tuohy needle is 2 and 3 mm, respectively. This suggests that dural tenting must occur at the time of either needle placement or epidural catheter insertion in neonates or infants. Ultrasound can determine the location of the catheter tip introduced via the sacral hiatus [178, 215].

Anatomical abnormalities [216, 218], particularly in those neonates with vertebral anomalies, unusual pits (Fig. 16.7), or tufts of hair suggesting an underlying spina bifida, can be identified using ultrasound. Anatomical abnormalities of the spinal cord (e.g., syrinx, diastematomyelia) can also be identified [216, 218].

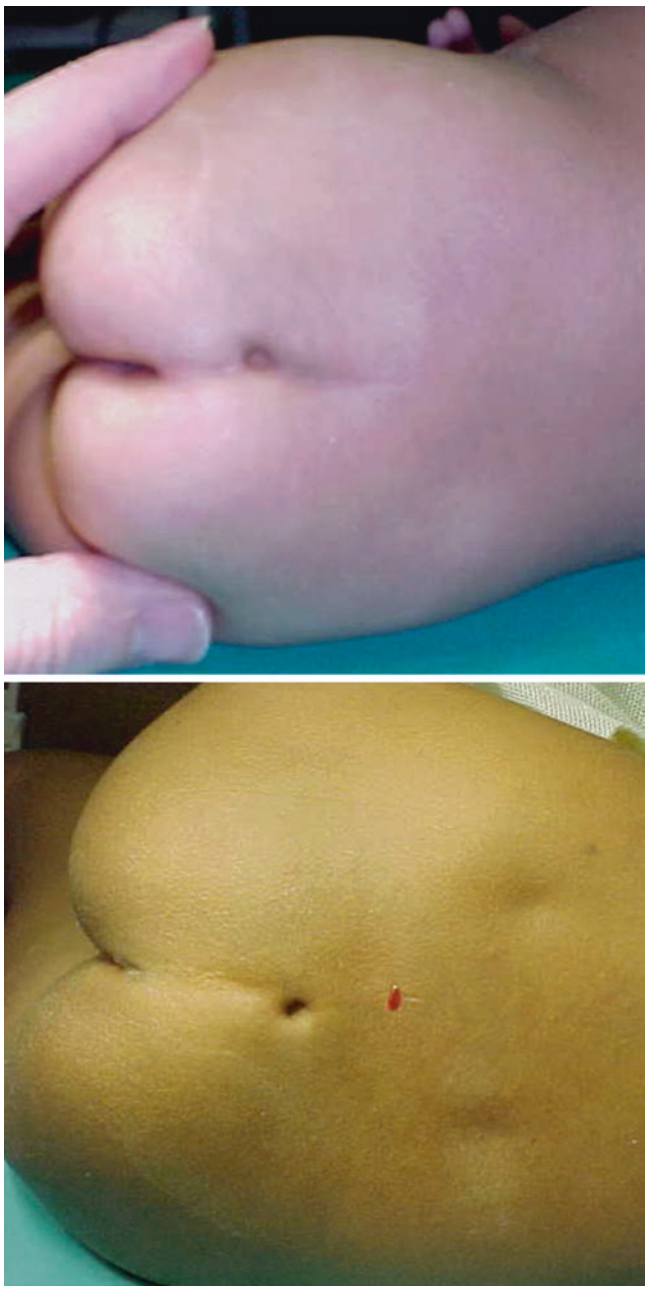

Fig. 16.7 Skin dimples or pits may indicate underlying spina bifida or cord abnormalities. Ultrasonography can be used to exclude these anomalies before placing either a caudal or epidural block

Peripheral Nerve Blocks

Peripheral nerve block can be performed in neonates [13, 14, 219–229] to provide analgesia postsurgery, for sympathetic blockade to facilitate PICC line placement [13, 14], or as part of the management of vascular complications [13, 14, 221, 225–227]. Nerve blocks can been placed using anatomical landmarks, a nerve stimulator [222], or ultrasound guidance [18, 220, 223]. These blocks are almost always placed under anesthesia or infrequently under awake/sedation in selected cases [7, 197].

Ultrasound guidance is the most accurate particularly when purely sensory nerves need to be blocked [215]. Peripheral nerves are less myelinated in neonates, and thus smaller concentrations of local anesthetic may be used to achieve a rapid onset of a block. For practical purposes, a dose of 0.1–0.2 mL/kg is sufficient to block most peripheral nerves.

Axillary blocks can be used to vasodilate veins to facilitate PICC line placement [13, 14] or to salvage an ischemic limb after misadventures with arterial catheterization [221, 224]. Larger concentrations speed the onset and provide motor block useful for PICC line placement in awake neonates [14], whereas smaller concentrations are adequate for sympathectomy and analgesia. Dose guidelines are 0.5–1.0 mL of a 0.125–0.5% bupivacaine, depending on the aim.

A **stellate ganglion block**, using a paratracheal approach onto Chassaignac's tubercle at the cricoid level, has also been used for this purpose [226, 227].

Femoral nerve blocks can also be used for PICC line placement in the lower limbs, muscle biopsy [219], skin graft, and clubfoot repair in infants. Successful placement of local anesthetic just lateral to the femoral arterial pulse can be achieved using anatomical landmarks, nerve stimulation, or ultrasound guidance. This block is relatively free of complications, but the hip's joint capsule deep to the artery may be entered.

Infraorbital nerve block: Although neonatal cleft lip repair (cheiloplasty) remains controversial (and is no longer performed in many institutions because the cosmetic result is not as good as originally thought) [228], an infraorbital nerve block provides excellent analgesia without the risk of respiratory depression [228–230]. This block may be particularly useful in infants with airway anomalies that could be compromised by opioids when used for cleft lip repair [230].

The infraorbital foramen is difficult to palpate in neonates and small infants. Two approaches have been described—a transcutaneous and an intraoral transmucosal approach. The nerve exits the infraorbital foramen, which is midway (15–17 mm) along a (30–34 mm) line drawn from the angle of the mouth to the midpoint of the palpebral fissure, approximately 7–8 mm from the alae nasi [228]. Using a 27–30 g needle, the nerve can be blocked by introducing a needle perpendicular to the skin to make bony contact close to, but not into, the foramen. The intraoral approach relies on the ability to palpate the foramen. A needle is introduced through the alveolar mucosal margin beneath the palpating finger. Both approaches provide analgesia with minimal risk of respiratory depression compared with fentanyl [229, 230].

Dosage: 0.5–1 mL 0.25–0.5% bupivacaine [228, 229], or ropivacaine, with 1:200,000 epinephrine.

Ilioinguinal nerve block provides comparable analgesia to caudal blockade for inguinal herniotomy or orchidopexy [231–233]. The ilioinguinal and iliohypogastric nerves lie between the transversus abdominis and internal oblique muscles 3–5 mm medial to the anterior superior iliac spine [91]. Under sterile conditions, a needle is introduced under ultrasound guidance in a medial to lateral direction, i.e., toward the iliac muscle and bone. The muscle layers in neonates are thin and compliant. The risk of penetrating the peritoneal cavity is much greater than in children if the needle is not advanced with caution [65].

When ultrasound is not available, identification of the "pop" as a short bevel needle penetrates the external oblique aponeurosis and internal oblique muscles is needed. These "pops" can be facilitated by introducing the needle at an angle—the greater the angle, the "thicker" the aponeurosis becomes. Large plasma concentrations of local anesthetics have been reported [231, 232], although this block is relatively free of complications. *Transient femoral nerve block* [234, 235] and *colonic perforation* have been described [65, 236].

Dosage: 0.1–0.2 mL.kg^{-1} 0.25–0.5% bupivacaine or 0.2–0.5% ropivacaine.

Transabdominal plane (TAP) block is becoming an increasingly popular alternative for intraoperative and early postoperative analgesia for selected procedures (ileostomy closure [237], colostomy [238] involving the abdominal wall [239, 240]. Under sterile conditions and using "in plane" ultrasound guidance, the lateral branch of the intercostal nerves can be blocked in the tissue plane between the internal oblique and transversus abdominis provided the spread of local anesthetic extends posterior to the midaxillary line. Hydro-dissection of this tissue plane confirms correct placement when introduced subcostally or above the iliac crest. The muscle layers are thin and compliant, and the risk of penetrating the peritoneal cavity, liver, or spleen is substantial if the needle is not advanced with caution. The needle tip must be visible at all times (see Fig. 16.8).

Dose: 0.2–0.5 mL.kg^{-1} of 0.25 bupivacaine or 0.2% ropivacaine.

Intercostal blocks can be placed under direct vision at surgery or using ultrasound guidance to provide analgesia after thoracotomy or chest tube placement in both cyanotic and acyanotic neonates.

Dosage: 0.6 mL/kg (1.5 mg/kg) of 0.25% bupivacaine with epinephrine [236]. Epinephrine should be added to all local anesthetics when used for intercostal block in order to minimize the risk of toxic plasma concentrations of local anesthetics (due to rapid absorption) and to prolong the duration of the intercostal blocks. Plasma concentrations using this dose are variable, but adverse events have not been reported [241].

Paravertebral block: Direct paravertebral placement of a catheter for continuous paravertebral block is technically difficult in neonates. [242, 243]. Extrapleural paravertebral placement under direct vision immediately before chest closure is a viable alternative for management of post thoracotomy pain. After an initial bolus of 0.5 mL.kg^{-1} of 0.25% bupivacaine, a continuous infusion of 0.125–0.25% bupivacaine at 0.2 mL.kg^{-1} h^{-1} with epinephrine provides satisfactory analgesia.

Erector spinae plane block (ESPB): This novel ultrasound-guided regional technique involves injecting local anesthetic deep to the erector spinae muscle at the lumbar or thoracic transverse process (Fig. 16.9) [244–246]. The spinal nerves are blocked as they leave the paravertebral space. Some retrograde spread to dorsal and ventral rami within the paravertebral space is thought to occur. ESPB is technically easier to perform and covers more dermatomes than a paravertebral block using the same dose (0.5 mL.kg^{-1} of 0.25% bupivacaine). ESPB has been used successfully for both thoracic and abdominal surgery [244–246].

Topical anesthesia: During the past two decades, there has been a substantial increase in the number and types of topical anesthetics [247]. Options for the prevention of neonatal pain associated with skin-breaking procedures were previously limited to injections of lidocaine. Topical anesthetics are now available as creams and gels and a heat-activated patch system [247]. The onset time varies for each modality, and careful planning is needed to coincide with the peak effect. Indications range from peripheral IV placement, lumbar puncture, circumcision, and heel sticks.

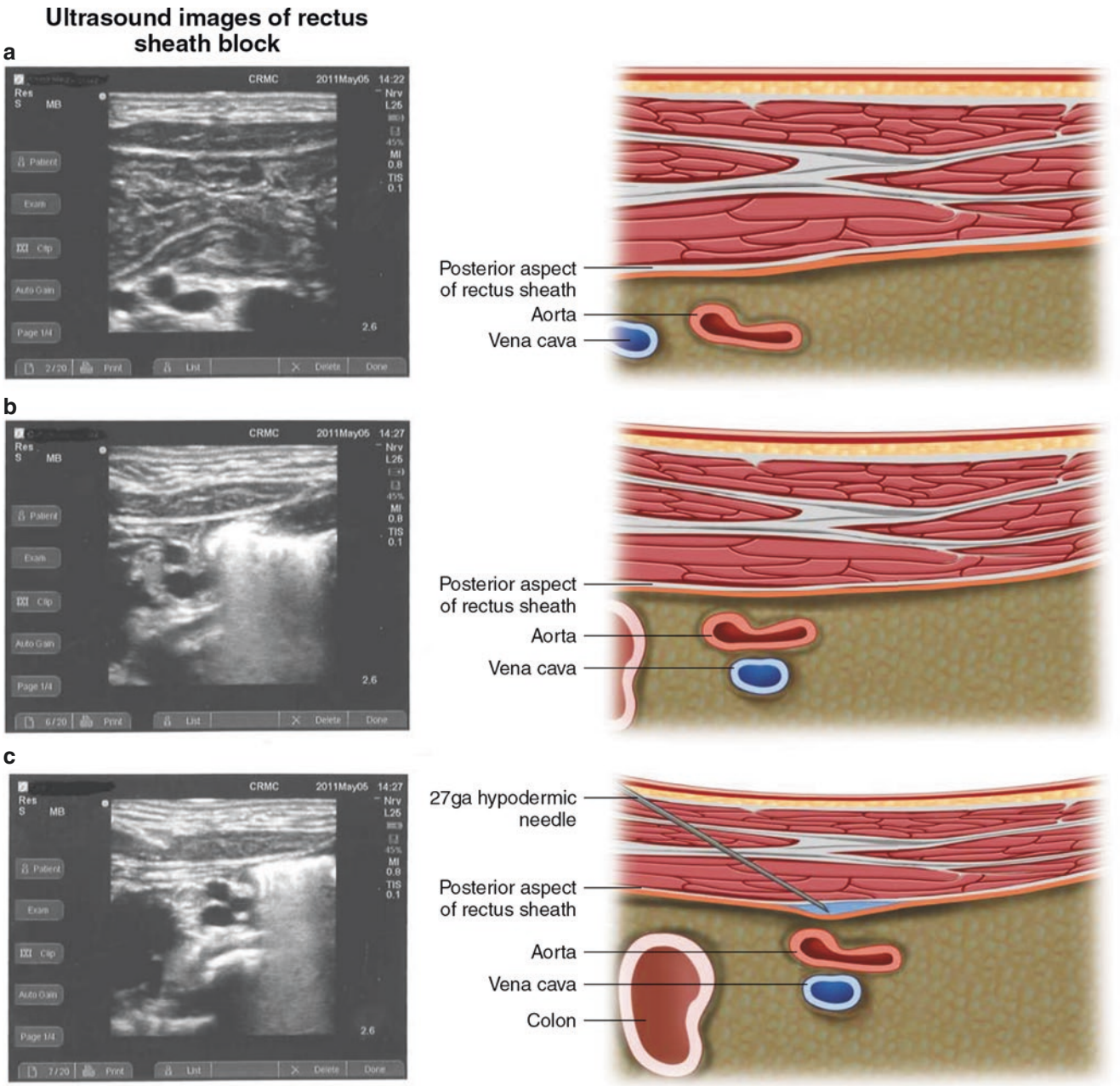

Fig. 16.8 Ultrasound images of the rectus sheath block through a compliant abdominal wall. (**a**) Before application of any pressure with the probe or needle. (**b**) With minimal pressure during needle insertion, the abdominal wall and rectus muscles can be pushed dangerously close to the aorta and inferior vena cava. (**c**) With pressure from the probe and the needle (visualized), the proximity of the needle tip as it approaches the posterior sheath to the aorta and vena cava is apparent

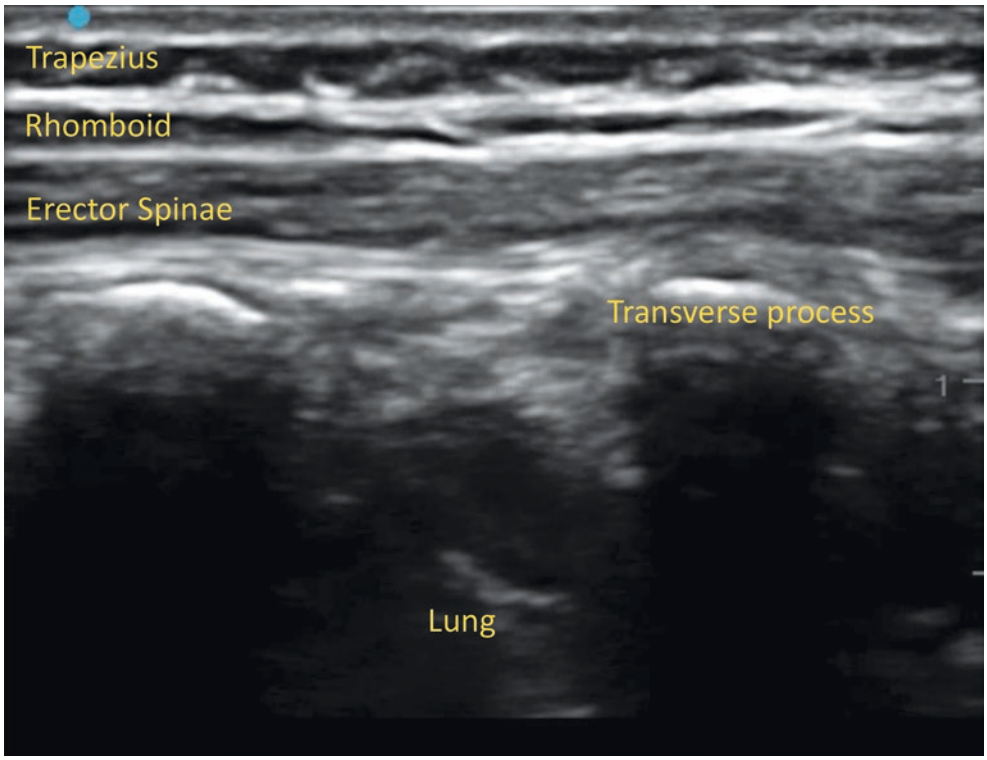

Fig. 16.9 Ultrasound image of the back muscles in a neonate. Muscles of the posterior chest are very thin. The trapezius is most superficial, the rhomboids are visible above T7, and the erector spinae muscle is deepest. The transverse process should not be confused with a rib since the ribs are flatter in neonates

Management of Local Anesthetic Toxicity

Neonates are more susceptible to local anesthetic systemic toxicity (LAST) than are older children. Prevention is therefore better than the cure since management of LAST in neonates may be difficult. A variety of drugs have been used with limited success in the past [248]. Recent reports of successful management using 20% lipid emulsion are encouraging [249–251].

Initial resuscitation should always proceed according to PALS guidelines, aiming to secure the airway, provide 100% oxygen, hyperventilate (to reduce the free fraction by inducing respiratory alkalosis), and provide circulatory support. Lipid emulsion (20% Intralipid®) should be given as soon as possible [252, 253]. An initial bolus of 1 mL/kg over 1 min, repeated at 3–5 min intervals (i.e. a total dose of 3 mL/kg), converting at that point, or earlier with evidence of recovery, to 0.25 mL/kg/h infusion once cardiovascular stability has been restored. Drugs (such as propofol) that are formulated in a lipid emulsion are not appropriate substitutes for Intralipid® particularly in the presence of cardiovascular collapse [254] (see Table 16.4).

There are a number of theories as to the mechanism of action of the lipid emulsion works: These include "(i) lipid sink" i.e. a distinct lipid compartment in the blood stream trapping lipophilic local anaesthetic agents (ii) at the mitochondrial level (interrupts fatty acid transport into cardiac mitochondria) and Intralipid supplies new energy (iii) activation calcium channels increasing intracellular calcium. To date, there have been in the order of ten case reports of intralipid use for LAST in children of which nine were successful.

Table 16.4 Management of LAST

1	Stop the local anesthetic infusion and call for help
2	Hyperventilate immediately with 100% oxygen
3	Suppress seizures if present (midazolam, thiopentone, propofol)
4	Begin external cardiac massage
5	Administer epinephrine 1mcg/kg or 0.1 mL/kg of 1:1000
6	Administer 1.5 mL/kg of 20% intralipid intravenously over 1 min. Follow it immediately with an infusion at a rate of 0.25 mL/kg/min. *Lipid emulsion in propofol should not be used in lieu of intralipid* a. Continue chest compressions (lipid must circulate) b. Repeat bolus every 3–5 min up to 3 mL/kg total dose until circulation is restored c. Continue infusion until hemodynamic stability is restored d. Increase the rate to 0.5 mL/kg/min if BP declines e. A maximum total dose of 10 mL/kg in first 30mins is recommended
7	If no response, consider ECMO if available

Conclusion

The benefits of regional anesthesia are significant, but safety should remain our primary concern particularly with today's high expectations and zero tolerance for morbidity after anesthesia. While most regional anesthetic techniques are simple to perform, they should never be considered routine because of the risks involved [7, 74]. Careful consideration of the indications and contraindications together with the setting (day case or hospital) should influence the decision. Continuous infusions and nerve blocks have limited duration. It is prudent to plan subsequent analgesia as part of a multimodal approach [255]. In general, the more peripheral the block, the lower the risk. Epidural anesthesia should be performed by, or under the guidance of, an experienced practitioner.

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17 Anesthetic Complications in the Neonate: Incidence, Prevention, and Management

Mary Lyn Stein, Robert F. O'Donnell, Monica Kleinman, and Pete G. Kovatsis

Introduction

The neonate is at risk for increased peri-anesthetic complications attributed, in part, to factors such as the transitional circulation and the immaturity of many organ systems and metabolic processes. Advances in perinatal and neonatal care together with the growing field of fetal interventions have increased the number of medically complex, preterm neonates presenting for anesthetic care. In the preterm neonate, incomplete maturation of all organ systems, particularly the pulmonary, cardiovascular, and neurologic, has further magnified the perioperative risks. Surgical or interventional procedures in neonates, such as repair or palliation of major congenital anomalies and management of life-threatening complications of prematurity, are rarely elective. Despite preparation, experience, and best intentions, peri-anesthetic adverse events confront all practitioners who care for neonates. Excellent communication and collaboration among the neonatal, anesthetic, and procedural teams are essential to optimize the outcomes for neonates.

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Peri-anesthetic Mortality and Adverse Events

The first reviews of perioperative morbidity and mortality in infants and children, which date back to the 1950s, reported a greater incidence of adverse events when compared with that in adults [1, 2]. In the first edition of Smith's text on pediatric anesthesia in 1959, he noted that greater than one-third of the deaths in children under 10 years of age occurred in neonates during the first week of life [3]. Reaching a similar conclusion, a report in 1961 suggested that the greater rate of cardiac arrest in children compared with adults could be attributed primarily to the greater frequency of arrest in infants [4]. In 1964, the Baltimore Anesthesia Study Committee estimated an anesthesia-related mortality rate of 3.3 per 10,000 children under 15 years old, with neonates accounting for a staggering 20.4% of these deaths [5].

The literature has consistently identified a greater rate of adverse events in infants compared with that in older children [4, 6–27]. However, most publications relied on self-reporting of the incidents and grouped the events that occurred in neonates with those in infants, without explicitly detailing the rate of adverse events in neonates. Underreporting is a common problem with self-reported events, which results in an underestimation of the true frequency of peri-anesthetic adverse events in the literature [28–31]. Some epidemiologic studies have relied on reporting critical incidents to a national database or reviewed closed claims. However, because these reports do not include a denominator, the frequency of critical events involving neonates remains elusive. Additionally, the lack of uniform definitions of clinical complications, regional differences in clinical practice, and the inability to control for or identify confounding variables can complicate the interpretation of adverse event studies. Studies from single institutions have the added challenge of accruing an adequate sample size to accurately reflect the frequency of rare adverse events. This may require collecting data for a greater duration. These issues limit the external validity of the data from individual

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institutions and direct comparisons among the studies. In 2015, a meta-analysis recommended a standardized reporting system for future studies of adverse events in pediatric anesthesia given the heterogeneity of existing data [32]. However, even with improved reporting, it is important to recognize that "there is probably an unknown and unquantifiable number of errors which may or may not be involved in a chain of events resulting in morbidity or mortality, but which go unnoticed and therefore unreported" [33].

The first prospective survey of pediatric anesthesia-related morbidity and mortality in 1988 included data from 40,240 anesthetics in children younger than 15 years from 440 randomly chosen institutions in France between 1978 and 1982 [8]. This survey included 27 major complications that were defined as fatal, life-threatening, or resulting in severe sequelae through the first 24 h after an anesthetic. The observed incidence of morbidity was 7 per 10,000 anesthetics with a mortality rate of 0.25 in 10,000. The risk of significant morbidity in infants (43 per 10,000) was greater than that in children 1–14 years old (5 per 10,000). Neonates were not analyzed as a group distinct from infants. Respiratory failure was identified as the most common cause of major complications in the infants, whereas respiratory failure and cardiac failure were equally responsible for major complications in older children. Higher ASA physical status, coexisting diseases, prior anesthetic exposure, and emergency surgery were all associated with an increased risk of complications.

In a retrospective review of anesthetic morbidity and mortality data from a single pediatric institution in Canada between 1982 and 1987, adverse events were collected for up to 72 h postoperatively in children less than 16 years of age. They included events that required an intervention intraoperatively by the anesthesiologists, selected events in the recovery room reported by the recovery room nurse, and any additional occurrences noted on chart review within 72 h of the procedure but without distinguishing if the events were related to the surgical procedure or the anesthetic. Of the 29,220 anesthetics that were reviewed, only 361 (1.2%) involved neonates, yet neonates experienced 41.5% of all events reported. Neonates experienced the greatest incidence of adverse events (83 per 10,000), 3 of which were intraoperative deaths. Neonates with complications were more likely to be ASA physical status 3 or greater and scheduled for major surgical procedures. In neonates, respiratory complications accounted for the majority of intraoperative events (54%), whereas blood pressure derangements (44%) and respiratory events (38%) accounted for the majority of events in the postoperative period. Of note, some events occurred more than once, and/or multiple events were observed in the same child but additional details were not provided. The researchers identified increased risks of hypothermia and cardiovascular instability during transport between the neonatal intensive care unit (NICU) and the ORs (operating rooms) in neonates <1 kg and modified their practice to perform selected procedures in the NICU [9].

The Canadian Pediatric Adverse Events Study described the epidemiology of adverse events among children in 8 academic pediatric centers and 14 community hospital in Canada between April 2008 and March 2009, selected randomly and evenly distributed across 4 age groups (0–28 days; 29–365 days; >1–5 years; and >5–18 years) [34]. There were 651 neonates of whom 29 (4.5%) experienced a total of 63 adverse events. Five of those neonatal adverse events (12.8%) were classified as surgically related adverse events. Anesthesia-related events were not specifically identified. Thus, it remains unclear if the anesthesia-related events were included in the surgical or the "other" group. Adverse events in the surgical category occurred less often in neonates when compared with all other age groups, and neonates in the NICU experienced significantly greater rates of adverse events than those not in a NICU. The latter may be related to the increased complexity of care associated with NICU patients, which parallels other reports [35, 36].

In a review of >100,000 anesthetics in children over a 5.5-year period, the 24-h mortality from any cause was 13 per 10,000 anesthetics, with a **15-fold greater rate in neonates** (180 per 10,000). Analysis of all deaths suggested that the rate attributable to anesthesia-related factors was small, ~1/10,000, with only one neonatal death in this category [26]. In another retrospective review of 45,182 anesthetics over 7 years at a tertiary pediatric hospital in the Netherlands, 72 neonatal deaths occurred within 30 days of 1862 neonatal procedures, with only 1 death attributable to anesthesia. This resulted in a 30-day anesthesia-related perioperative mortality rate of 5.4 per 10,000 in neonates [27].

Pediatric perioperative mortality associated with major surgical procedures (excluding cardiac and trauma operations) has been reported from the Pediatric Participant Use Data File (PUF) collected between 2012 and 2015. The overall 30-day perioperative mortality rate in infants and children was 70 per 10,000. The results were not stratified by age. Given that the procedures necrotizing enterocolitis (NEC) and congenital diaphragmatic hernia (CDH) were associated with the greatest proportion of perioperative mortality (19% and 5%, respectively), we can deduce that this mortality most likely occurred in neonates and infants. Additionally, 67% of perioperative mortality associated with NEC occurred within 24 h of the procedures. Perioperative mortality of NEC was strongly associated with sepsis along with the need for inotropic support and blood transfusion within 48 h of surgery [37].

A single-center quality improvement study demonstrated that the incidence of adverse events in neonates and infants

was greater than in older children, irrespective of the location (OR versus nonoperating room). Respiratory events were the most common cause of adverse events [24].

The Pediatric Risk Assessment (PRAm) score is a tool devised to predict the perioperative risk of mortality in pediatric patients undergoing noncardiac surgery. The PRAm score originated from the pediatric database of the American College of Surgeons (ACS) National Surgical Quality Improvement Program to predict 30-day mortality in patients 18 years of age and younger [38]. The score, which ranges from 0 to ≥9, is the sum of surgical urgency (one point); presence of any significant comorbidities (two points); factors of critical illness such as mechanical ventilation, inotropic support, or cardiopulmonary resuscitation (three points); age less than 12 months (three points); and the presence of a neoplasm (four points). A PRAm score ≥ 6 confers an eightfold increase in 30-day mortality for patients with an American Society of Anesthesiologists physical status (ASA PS) of ≤3 [39]. The PRAm score may contribute to the prospective assessment of risk during the peri-anesthetic care of neonates, but this remains to be established.

Despite differences in study design, data sets, and analyses, a large body of research [10–12, 14–18, 20, 22, 40] supports the general findings of the studies discussed in detail in the proceeding section, leading to the following conclusions:

1. Risks are greater in infants and more specifically in neonates.
2. Respiratory and airway-related events are the leading categories of adverse events.
3. Factors such as comorbid disease (ASA physical status 3–5) and emergency surgery increase the risk in the perioperative period.

Peri-anesthetic Cardiac Arrest

Cardiac arrest during pediatric anesthesia is a sentinel event. Depending on the population studied, the reported incidence is between 1.4 and 147 per 10,000 anesthetics, with an associated mortality rate between 5 and 28% [1, 13, 19, 21, 23, 25, 41–45]. The Pediatric Perioperative Cardiac Arrest (POCA) Registry, a voluntary reporting system of intraoperative cardiac arrests in children, was established in 1994 by the ASA Committee on Professional Liability and the American Academy of Pediatrics Section on Anesthesiology [13]. In their initial review of submitted data of the first 4 years, neonates accounted for 15% (22/150) of all anesthesia-related cardiac arrests and 26% (75/289) of all cardiac arrests [13]. Their analysis concluded that cardiac arrest occurred most often in infants, <1 year of age, with the most common causes of arrest being medication-related and cardiovascular. ASA physical status 3–5 and emergency surgery were predictors of mortality, but age was not. In a follow-up analysis of the POCA Registry between 1998 and 2004, neonates accounted for 11% (21/193) of all anesthesia-related cardiac arrests, which was similar to the incidence reported previously [19]. Specific analyses of neonatal cases were not performed. ASA physical status 3–5 and emergency surgery remained predictors of mortality with medication-related causes of cardiac arrest decreasing significantly, attributable to the decreased use of halothane.

In a single-institution retrospective review of anesthetics between 2000 and 2011, cardiac arrest occurred in 5.1 of 10,000 anesthetics, with 2.6 per 10,000 classified as anesthesia-related [43]. Age ≤6 months was significantly associated with the incidence of anesthesia-related cardiac arrest.

In 2017, a prospective cohort study (the Anaesthesia PRactice In Children Observational *Trial* (APRICOT)) from 261 participating facilities in 33 European countries captured 31,127 anesthetics in 30,874 children over a defined 2-week period [44]. The cases were assessed for severe perioperative critical events that required immediate intervention that (may have) led to death or major disability. The overall incidence of severe perioperative critical events was 5.2%, with an increasing incidence with decreasing age. Respiratory events were the most likely proximate cause. In our interpretation of the published data from the neonatal subgroup, the overall rates of critical events were greater in this age group, with a primary cardiovascular etiology four times greater (12%) than a respiratory etiology (3%). The data demonstrated a large variability in pediatric anesthetic practice among institutions as well as a relatively high rate of critical events. The incidence of critical events for providers with a greater experience (in terms of years in anesthesia practice) was statistically significantly less than for those with less experience. The APRICOT study supports further education and quality improvement strategies targeting pediatric anesthesia care teams. The study also supports the benefit of universal practice standards, active support of peripheral hospitals by specialized pediatric centers, and matching complex and high-risk cases with anesthesiologists with commensurate experience and training [44, 46].

Wake Up Safe (WUS) (http://wakeupsafe.org/) is a patient safety organization and quality improvement initiative sponsored by the Society of Pediatric Anesthesia (http://www.pedsanesthesia.org/) and certified by the Agency for Healthcare Research and Quality (AHRQ). The WUS registry collects serious adverse events associated with pediatric anesthetics from its member institutions [47]. This registry overcomes many of the limitations of single-institution studies and other databases that do not include reliable demo-

graphic information. Reports from WUS have substantiated the notion that infants are at a greater risk for a variety of adverse events including transfusion-associated hyperkalemic cardiac arrest [48] and cardiopulmonary arrest in the PACU [49]. An analysis of the WUS cases submitted between 2010 and 2015 revealed that the incidence of cardiac arrest in infants <6 months of age was threefold greater than in those >6 months of age and children. Neonates, who comprised only 17% of the total number of cardiac arrests, appeared less likely to survive the cardiac arrest, accounting for 31% of the non-survivors [45].

Postoperative cardiac arrest is a significant risk factor for mortality among many subgroups including neonates with congenital heart disease. Researchers used the POCA registry to compare cardiac arrest in children with and without heart disease. Those with cardiac disease were more likely to experience an arrest from a cardiac cause (50% vs. 38%), and the arrest was more likely to occur in the general OR (54%) than in the cardiac OR (26%) or catheterization laboratory (17%). There were no data related specifically to neonates, although a significant number of events occurred in infants <6 months of age [25]. A single-institution, retrospective review of cases from 1988 to 2005 reported that the frequency of cardiac arrest and associated mortality in neonates undergoing cardiac surgery was more than nine times the rates in neonates undergoing noncardiac surgery [21]. In another single-institution study of infants with congenital heart disease who suffered perioperative cardiac arrest during cardiac surgery, the risk of anesthesia-related cardiac arrest was greater than reported in the general pediatric population. In this study, neonates with congenital heart disease had a greater incidence of anesthesia-related cardiac arrest than older children [23]. When cardiac arrest occurs after complex cardiac surgery, mortality was almost twofold greater in low-birth-weight (LBW) neonates (defined as <2.5 kg) than in the general population of neonates (12.1% vs. 6.8%, respectively) [50].

There is scant literature on the rate of postoperative cardiac arrest in the NICU. In a large series of pediatric intensive care unit patients who suffered cardiac arrest, survival to discharge for neonates was 27% [51]. A more recent single-center report found an incidence of cardiac arrest in a quaternary NICU to be 1.2 events per 1000 patient-days or 2.2% of admitted patients. Survival to discharge was 61% [52].

Respiratory and Airway Complications

Studies have consistently demonstrated that airway and respiratory events are among the most common complications during pediatric anesthesia, with laryngospasm and/or "airway obstruction" occurring most frequently [11, 15, 17, 22, 24, 25]. Not surprisingly, respiratory complications and loss of the airway are the most common adverse events associated with anesthesia in neonates and infants [53]. Laryngospasm is the leading cause of cardiac arrest in the respiratory subgroup from the POCA registry [13, 19]. A study of the incidence of laryngospasm in all ages reported that the greatest risk occurred in infants 1–3 months of age [6]. An observational analysis of NICU patients recovering in the PACU found a significant association of serious adverse events with birth weight less than 1.58 kg and post-menstrual age at surgery <41 weeks. If a patient had both factors, the risk of a serious adverse event increased by a factor of 7. All the serious adverse advents were respiratory [54].

The POCA registry identified that 27% of reported cardiac arrests were respiratory-related and most commonly associated with laryngospasm and airway obstruction [19]. Recognizing this, Cincinnati Children's Hospital implemented a quality improvement project over 2.5 years to increase the availability of airway emergency drugs (succinylcholine and atropine), the use of non-depolarizing muscle relaxants for endotracheal intubation in children 2 years of age and younger, and the presence of anesthesia providers until emergence from anesthesia in high-risk patients. By the end of the project, the incidence of serious airway events was reduced by 44%, and that of airway cardiac arrests was reduced by 59% compared with the preceding 2 years [55].

In neonates and young infants, the combination of pronounced airway protective reflexes, smaller airway caliber, and noncalcified chest wall increases the risk of airway obstruction during inspiration [56]. Even during "normal breathing," the compliant chest wall of neonates and infants lowers transpulmonary pressures and lung volumes, which increases the tendency toward airway collapse. Because of this propensity for obstruction at static functional residual capacity (FRC), infants (and neonates in particular) need to maintain a dynamic FRC. Early diaphragmatic contraction and laryngeal "braking" (vocal cord adduction) during expiration generate dynamic FRC by supporting a greater lung volume during the respiratory cycle. These developmental mechanical properties, coupled with high oxygen consumption, increase the risk of perioperative hypoxemia and hypercapnia and postoperative respiratory events in neonates [9].

Sedatives and anesthetics impair or ablate the neonate's capacity to sustain respiratory adaptations. During the delivery of anesthesia, the provider can compensate by using continuous positive airway pressure (CPAP), assisted ventilation, or controlled ventilation with positive end-expiratory pressure (PEEP) to avoid respiratory deterioration. Extremely preterm infants who require mechanical ventilation should be closely monitored to maintain FRC without overdistention. If the alveoli are overdistended, then it could lead to lung injury, resulting in respiratory distress syndrome and lasting bronchopulmonary dysplasia (BPD) and chronic lung disease [57]. A Cochrane review concluded that lung-

protective ventilation with volume targeted ventilation in preterm infants less than 44 weeks corrected gestational age decreased the incidence of BPD and death when compared with pressure-limited ventilation [58].

Many neonates exhibit periodic breathing, that is, relative tachypnea with interspersed periods of apnea not associated with bradycardia and/or significant hypoxemia [59, 60]. Significant or pathological apnea is defined by the cessation of breathing for more than 15 s or for any duration when it is accompanied by bradycardia or cyanosis. This is particularly common in preterm neonates [60, 61]. Respiratory control in the neonate is characterized by blunted responses to hypoxia and hypercarbia. The hypoxic response is biphasic with the initial response being hyperventilation followed by hypoventilation, bradycardia, and apnea if the hypoxia is not remedied quickly (see Chap. 2). Residual trace concentrations of inhalational anesthetics may abolish the initial hyperventilation response to hypoxia in the neonate. The risk of perioperative apnea is increased when hypothermia, metabolic derangements, sepsis, lung disease, and residual anesthetics are also present. Anemia remains controversial with a recent study failing to demonstrate an association with apnea, although that study was not powered to demonstrate an effect of anemia [62]. Adaptive responses to hypoxia and hypercarbia are further blunted in the perioperative period and in preterm infants, increasing the risk of respiratory complications in the form of apnea and hypoxemia.

Postoperative apnea in the preterm neonate and infant may also exhibit an obstructive component since residual anesthetic agents depress upper airway muscle tone as well as the respiratory coordination needed to maintain the upper airway [63]. Neonates are also more prone to upper airway obstruction related to head and neck position, which is more likely to occur with residual anesthetics and analgesics.

In 1982, a retrospective analysis of the risk of perioperative apnea after hernia surgery in preterm and full-term neonates and infants reported a 20% incidence of perioperative apnea in preterm neonates compared with zero events in full-term neonates [64]. This prompted eight prospective trials that culminated in a combined analysis in 1995 that determined that "apnea was strongly and inversely related to both gestational age and postconceptional age" with associated risk factors of ongoing preoperative apnea and anemia [65]. The authors concluded that the incidence of apnea decreases to less than 1% beyond a postconceptional age of 54–56 weeks, but the external validity of this conclusion has been questioned [66].

It is well established that neonates, preterm neonates, and ex-premature infants require postoperative monitoring for apnea and bradycardia. Many clinicians advocate regional anesthesia without parenteral or oral sedation in neonates, especially premature neonates, to minimize the risk of postoperative apnea. Most institutions recommend that term infants less than 44 weeks postconceptional age and ex-premature infants less than 60 weeks postconceptional age be admitted postanesthesia for a minimum of 12 h apnea-free continuous monitoring. If the infant experiences an apnea, he/she should continue to be monitored. Others recommend that all infants less than 46 weeks postconceptional age be admitted for a minimum of 12 h of apnea monitoring postoperatively and those between 46 and 60 weeks postconceptional age be evaluated and if comorbidities such as a history of apnea, chronic lung disease, neurological disorder, or anemia are present, then they too should be monitored continuously for 12 h [67]. All other healthy neonates beyond 4 weeks postnatal age should be scheduled first on the surgery list and monitored for 6 h postoperatively for apnea.

Regional anesthesia (spinal, caudal, or spinal and caudal without additives other than epinephrine) in ex-premature infants is an effective alternative to general anesthesia. However, if any sedation is administered, the incidence of perioperative apnea will be similar to that after a general anesthetic [68–71]. In a direct comparison of spinal and general anesthesia, spinal anesthesia did not reduce the risk of central apnea in preterm infants, although there was less desaturation and bradycardia in the perioperative period [72]. Spinal anesthesia that requires supplemental sedatives or a partially failed spinal that requires general anesthesia may be associated with a high risk of postoperative apnea [73, 74]. These publications also postulated that infants with a postconceptional age of approximately 41 weeks or less have an increased risk of delayed postoperative apnea, particularly when comorbidities are present. A more recent study of apnea using data from the General Anesthesia compared with Spinal Anesthesia (GAS) study determined that the overall incidence of apnea after regional and general anesthesia were similar. However, apnea was a secondary outcome in the GAS study, and the study excluded many infants who were extremely premature and those with comorbidities, was not powered to differentiate the incidence of apnea between general and regional anesthesia, and did not require a uniform monitoring strategy for apnea postoperatively. Nonetheless, a subgroup analysis revealed that apnea with regional anesthesia was less than with general anesthesia in the early postoperative period, from 0 to 30 min after surgery [62]. The incidence of postoperative apnea was 6% in ex-premature infants, consistent with the literature [65]. Interestingly, interventions including positive pressure ventilation and CPR were required in 1.3% of infants, with six of the nine interventions occurring in PACU, within 30 min of the end of surgery and all in infants who received general anesthesia. Prematurity was the strongest predictor of apnea in the GAS study as 96% (24/25) of infants with apnea were born preterm.

The least-soluble, potent inhalation agent, desflurane, facilitates a rapid emergence from anesthesia and may

decrease the risk of postoperative apnea when combined with a regional technique [75–77]. However, the evidence remains insufficient to support such a claim. Given the failure rate and relative stress of awake regional techniques, using dexmedetomidine as a sedative to facilitate the placement of the regional anesthesia and possibly reduce the stress response may be an alternative technique without increasing the need for peri-anesthetic respiratory intervention [78, 79]. In a prospective study of general anesthesia (GA) versus combined spinal-epidural anesthesia (CSEA) in 50 infants at a mean age of approximately 6 weeks and postconceptional age of 48.5 (GA) and 46.1 (CSEA) for gastrointestinal surgery, the incidence of adverse cardiorespiratory events in the first eight postoperative days in the GA group was significantly greater than in the group receiving CSEA [80]. Of note, the infants who received GA were treated with a fentanyl infusion for postoperative analgesia, whereas the CSEA group received a continuous infusion of bupivacaine via the thoracic epidural catheter. The postoperative analgesic regimen may have contributed to the increased incidence of adverse cardiorespiratory events in the GA group.

Methylxanthines such as caffeine reduce but do not eliminate the risk of postoperative apnea in preterm infants. They may be administered when neonates present to the OR with continued apnea or have apnea postoperatively [81, 82]. Methylxanthines also reduce the rate of extubation failure in preterm infants in the NICU, but not specifically in the post-anesthetic period [83]. A systemic review of meta-analyses which were considered limited in quality showed the non-inferiority of caffeine to doxapram or other methylxanthines in the management of apnea of prematurity [84].

Polymorphisms in the adenosine1 receptor gene may explain interindividual variability in response to caffeine: infants >28 weeks' gestation who responded to caffeine carried the rs16851030 C/C A1 genotype [85]. A large, retrospective study concluded that sex-based differences occur in apnea of prematurity such that females may have more rapid maturation of the respiratory system [86]. Further studies are warranted to explore the possible role of adenosine polymorphisms and sex in a larger population of preterm infants as they relate to the risk of apnea of prematurity.

The pediatric airway literature strongly suggests that multiple attempts at tracheal intubation in infants and neonates increase the frequency of complications. A retrospective analysis of 1341 infants revealed that 16% required two or more laryngoscopy attempts to achieve tracheal intubation and those who required additional attempts had a significantly greater rate of hypoxemia than infants who required a single attempt [87]. Similarly, in another retrospective study in which induction techniques for pyloromyotomy were compared, multiple attempts at tracheal intubation were associated with an 11-fold increased odds of hypoxemia compared with a single attempt and an 18-fold increased odds in neonates [88]. The Pediatric Difficult Intubation Registry (PeDI-R) reported that >2 intubation attempts and infants who weigh <10 kg correlated with a significantly increased risk of complications [41]. Subsequently, the PeDI-R concluded that each additional intubation attempt increased the risk of complications by twofold [89].

Neonates can develop stridor after tracheal extubation, although the incidence is not well-documented. Systematic reviews, including neonatal studies, have consistently shown that neither IV steroids nor nebulized racemic epinephrine prevents post-extubation stridor [90–93].

Acquired subglottic stenosis is also a known complication of prolonged tracheal intubation in the neonate. The incidence of subglottic stenosis after tracheal intubation in the neonate ranges from 1 to 8% [94–96], with a gradual decrease in the incidence over time [97–99]. Prolonged duration of intubation and reduced birth weight increase the risk for subglottic stenosis [96, 100]. In a large series of pediatric patients undergoing cardiac surgery, the incidence of subglottic stenosis was 2.3% in infants <1 year of age. The duration of tracheal intubation being >96 h was a risk factor for subglottic stenosis. However, the incidence of subglottic stenosis in neonates undergoing congenital heart surgery whose airways were intubated with cuffed versus uncuffed tracheal tubes did not differ significantly [101]. A retrospective, case-control study from a single institution reported an overall incidence of subglottic stenosis that required surgical intervention in children without genetic syndromes to be 0.93%. The incidence was nearly 4% in infants <28 weeks' gestation compared with 0.13% in those ≥28 weeks. Multivariate analysis identified the following three factors that were associated with the development of subglottic stenosis: more than five previous intubations (aOR 3.74; 95% CI 1.15 to 12.19), a traumatic intubation (adjusted OR (aOR) 3.37; 95% CI 1.01 to 11.26), and a ratio of the internal diameter (mm) of the tracheal tube/gestational age > 0.1 (aOR 6.40; 95% CI 1.65 to 24.77) [99].

Oral or airway stimulation may lead to vagally mediated mild or severe bradycardia and even to asystole and apnea [102–104]. This response may be further enhanced in the setting of hypoxia [105]. In early reports, the use of halothane likely contributed to the incidence and severity of bradycardia at induction of anesthesia and with airway management. Now that halothane has been supplanted with sevoflurane, anticholinergic pretreatment is generally unnecessary unless a vagotonic medication such as succinylcholine is also administered [106, 107]. There have been reports of a decreased incidence of intraoperative bradycardia in infants from pre-2000 (127 per 10,000 anesthetics [16]) to post-2000 (33 per 10,000 anesthetics [13]), which may be attributable to the transition from halothane to sevoflurane; however, establishing causality is difficult based on the available data.

Pulmonary aspiration of gastric contents in the perianesthetic period is a rare but potentially fatal complication. The reported incidence of aspiration in infants ranges from 3.6 to 10.2 per 10,000 [8, 17, 20, 108–110]. One study reported that the incidence of pulmonary aspiration during emergency procedures exceeded that of non-emergent ones, with the majority occurring at induction of anesthesia [109]. In contrast, an analysis of over 50,000 anesthetics demonstrated that although the risk of aspiration was marginally increased under emergency conditions, it correlated most closely with ASA physical status [108]. These studies found no instances of aspiration in neonates. Neither study considered any of the infants and children who aspirated to have had serious morbidity, despite a few requiring prolonged post-aspiration ventilator support. While severe morbidity and mortality were unlikely after aspiration, closed claims analysis and national databases revealed that aspiration is a reported cause of serious untoward complications [10, 22, 111].

Residual muscle weakness after antagonizing the neuromuscular blockade may also pose a significant risk of adverse events in neonates. This risk may be exaggerated in neonates with respiratory disease or congenital and acquired anatomic airway abnormalities. The use of a safe and effective agent to antagonize neuromuscular blockade would minimize the adverse events that may result from residual neuromuscular blockade. Sugammadex may be an optimal drug to antagonize aminosteroid neuromuscular-blocking agents. It is capable of completely antagonizing even profound neuromuscular blockade by trapping the aminosteroid in a cyclodextrin toroid; it has a compelling and growing safety profile compared with using both an anticholinergic and an anticholinesterase. A 2019 retrospective review found that the incidence of adverse events such as bradycardia and anaphylaxis between neostigmine and sugammadex was not different [112]. Although all children recovered after sugammadex more quickly than after neostigmine, the greatest difference in the speed of recovery occurred in neonates with an almost 12-min faster recovery time after sugammadex. Today, the use of sugammadex in neonates remains off-label. Evidence supports the use of sugammadex in children >2 years of age; however, evidence of sugammadex's safety and efficacy in neonates remains limited [113].

Additional Considerations

Location of Operative Procedures

The traditional location for providing anesthesia and performing major surgical procedures has been the OR. The purported benefits and advantages include the OR team, efficiencies in care and supplies, a more aseptic environment or the ability to provide and maintain such an environment, and the preservation of a familiar, comfortable surgical setting. Over the past few decades, the practice of performing surgery in neonates in the NICU has gained favor by mitigating the risk of transport, especially for preterm neonates and those more critically ill. Procedures performed in the NICU include abdominal procedures for NEC, cryotherapy for retinopathy of prematurity (ROP) [114], cannulation for extracorporeal membrane oxygenation (ECMO), and less commonly, balloon atrial septostomy [115] and ventriculosubgaleal shunts for posthemorrhagic hydrocephalus [116].

Transporting neonates, particularly critically ill neonates, between hospital locations has many potential dangers, particularly for the extremely preterm infant and those who depend on high frequency ventilation (see Chap. 13, Anesthesia Outside the Operating Room). During transport from the stable, safe environment of the NICU or OR, the critically ill neonate is vulnerable to a number of mishaps including equipment failure, disconnections from drug infusions and equipment, temperature instability, and even provider distraction as they deal with navigating through doors, elevators, and hallways. If sophisticated NICU ventilators are not available for transport, the critically ill neonate is left with less than ideal ventilation techniques during transfer. A single-institution study reported a 27% incidence of complications in 1197 intrahospital NICU transports. Increased risk for complications was associated with surgical transports, pre-transport assisted ventilation, pre-transport supplemental oxygen, central nervous system malformations, and longer duration of transport [117]. A WUS review reported that 5% of the reported pediatric events were transport-related and of these transport-related events, nearly 40% occurred in infants <6 months of age, even though this age range represented only 7% of the database [118]. They found 13 transport-related deaths, 3 of which were in neonates, underscoring the vulnerability of neonates. The study authors found that a personal and institutional learning curve occurred over the study period with ongoing improvements in human and environmental factors.

In many institutions, surgical procedures are either routinely performed in the NICU, or the option exists if the risk of transporting the patient outside of the NICU is determined to be excessive. A 1993 report described the characteristics and outcomes of 193 neonates who underwent surgery either in the NICU or in the OR. Not unexpectedly, infants with a greater acuity of illness, as evidenced by the preoperative requirement for mechanical ventilation, underwent surgery in the NICU [119]. Likewise, surgical procedures performed in the NICU, as opposed to the OR, involved neonates with reduced birth weights and gestational age. Overall, the mortality in the NICU surgical group was greater than in the OR group (14% vs. 2%, respectively), which may be attributed to sicker neonates undergo-

ing procedures in the NICU versus the OR. Of note, neonates were more likely to become *hyper*thermic (>37.5 °C) in the OR than in the NICU likely due to the presence of forced air warmers and other external heating devices in the OR. In two reviews comprising >80 neonates who underwent a variety of surgeries in the NICU, there were no anesthesia-related deaths [120, 121]. In a single-center retrospective study, the surgical complication rate for patent ductus arteriosus ligation in the NICU (9%) did not differ significantly from the same surgery performed in the OR (8%), with no deaths related to the procedure [122]. The surgeons traveled to off-site NICUs for the procedures, which avoided the complexity of transporting NICU infants between hospitals. In another series of 42 neonates with congenital diaphragmatic hernia who required HFOV, the mortality associated with surgical repair performed in the NICU did not differ from that in the OR [123]. In a retrospective analysis of 233 neonates who required laparotomy for NEC, the mortality in infants <1500 g who underwent surgery in the NICU because they were judged to have significant risk if transported to the OR did not differ from those who were operated on in the OR [124]. In the previously discussed, single-center, retrospective Dutch study, the majority of deaths (84%) occurred during procedures in the NICU or PICU despite making up less than 10% of the overall procedures reflecting the severity of illness in such patients deemed too ill to transport to the OR [27].

In a prospective, case-control study that included 108 infants from a single institution who were sequentially scheduled for an operative procedure in the OR (55) or the NICU (53), clinical perioperative hypothermia in neonates undergoing surgery in the OR (65%) occurred 7 times more frequently than in those undergoing surgery in the NICU (13%) [125]. The hypothermic neonates in both groups required more interventions for respiratory and cardiac support. Instituting a multidisciplinary transport protocol that included a discrete checklist, team education, ongoing monitoring with periodic feedback, and rapid cycle reiterative improvement decreased the frequency of perioperative hypothermia in those transferred from the NICU [126]. The Children's Hospitals Neonatal Consortium developed the Perioperative Euthermia Clinical Practice Recommendations to maintain euthermia in neonates undergoing procedures [127]. The recommendations include establishing euthermia before the procedure and standardizing practice to maintain the neonate's temperature during transport to and from the NICU and during the surgery. These 19 institutions were able to reduce postoperative hypothermia by 48% by employing two key strategies: [127]

1. Compliance with ensuring neonatal euthermia defined as 36.1–37.9 °C on transfer and arrival to and departure from the OR.
2. Prewarming the OR temperature to >23.3 °C (74 °F). Of note, the frequency of hyperthermia increased significantly but not clinically from 1.1% to 2.2%, without any sequelae.

The Consortium concluded that interdisciplinary team engagement and high compliance to processes throughout the procedure period together with identifying the opportunities and barriers within each system were essential.

In a retrospective study of infants in a tertiary care NICU, surgical site infections occurred in 4.3 per 100 interventions (CI 95% 3.2 to 5.7), a rate similar to the general pediatric population. Very low-birth-weight (VLBW) infants and those undergoing gastroschisis closure are at greater risk for surgical site infections [128]. A single-institution, prospective, cohort study found the overall incidence of surgical site infections in neonates was 43/319 (13.5%) and identified a preoperative NICU stay of ≥4 days and gastrointestinal procedures as independent risk factors [129]. Concerns have been raised about the ability to create and maintain an aseptic environment for surgical procedures in the NICU environment compared with the OR. Retrospective analyses of the rates of infection and sepsis in infants undergoing procedures in the NICU or the OR yielded mixed results [119, 123]. Evidence for periprocedural antibiotic use in neonates remains inadequate. Moreover, data suggest that antibiotics are overused [130]. Institutions should consider forming interdisciplinary antimicrobial stewardship teams to develop appropriate plans to identify and treat at-risk infants using local data to select, monitor, and optimize the therapy [130–132].

Between 1999 and 2009, general surgical cases in the NICU at a single institution were reviewed. Neonate whose airways were already intubated and were ventilated remained in the NICU for their surgeries; the remainder traveled to the operating room. The authors reported that more than one-third of the general surgeries or 36% of the 859 total surgeries were performed in the NICU compared with almost two-thirds or 64% that were performed in the operating room. There were no surgical complications noted in the NICU cases with only a single adverse event of an operative delay while awaiting equipment. For the last 6 months of the study, the team compared operations performed in the NICU (n = 21) with those in the ORs (n = 7) prospectively and evaluated temperature, infectious complications of surgery, and adverse events related to transfers. They found no difference in these parameters except for one event in which intravenous access was lost during transfer back to the NICU [133], although the sample size for the prospective portion of the study was insufficient to identify differences between the outcome variables.

Before traveling between the NICU and a procedural area, providers should ensure that the appropriate equipment

and supplies are present and functional, including an adequate supply of supplemental oxygen. The transport team should review roles and plans for potential adverse events. Physiologic monitoring should be maintained at a level similar to that in the NICU/OR environment to facilitate early detection of any clinical issues. The use of a transport incubator supports thermoregulation but may impair the team's ability to visualize and access the infant. Given these risks, in the case of extremely ill neonates, a multidisciplinary team meeting should be convened to determine the location and details relative to the surgical procedure to optimize the care provided.

Transfusion of Blood Products

Transfusions are frequently required for critically ill neonates undergoing anesthesia for surgical conditions. Although the measured volume of blood loss may be small, any blood loss is a proportionally greater fraction of the circulating blood volume in neonates. Thus, meticulous attention must be paid to the amount of blood harvested for laboratory studies and the amount lost during surgeries. Red blood cell transfusion may be considered for preterm neonates who require mechanical ventilation for hemoglobin levels of less than 12 g/dL while allowing for reduced thresholds in neonates who do not require mechanical ventilation, specifically hemoglobin transfusion thresholds of 7–10 g/dL, with variation for gestational and postnatal age as well as underlying disease process [134, 135]. Children with preoperative anemia demonstrated an increased risk of in-hospital mortality, but whether any correction of preoperative anemia improves patient outcomes and if this finding also applies to neonates remain unclear [136–138]. For procedures that are associated with significant blood loss (e.g., >40 mL/kg), we advise the following processes to minimize exposure and known complications: use blood conservation techniques such as cell salvage and antifibrinolytic medications; transfuse the freshest units of packed red cells possible (<7 days old) or use washed units; and minimize the interval between irradiation of the blood to its administration (less than 24 h) [139–144].

Neonates are particularly vulnerable to transfusion-related complications including hyperkalemia, hypothermia, and citrate-induced electrolyte alterations (ionized hypocalcemia and hypomagnesemia). Hyperkalemia has been a leading cause of cardiac arrest under cardiovascular causes in the POCA registry [19]. Potassium accumulates in the acellular fraction of packed red blood cell units as it leaks from red blood cells that have been stored for a prolonged period, increasing linearly with the number of days of storage. Hyperkalemia may also be present in plasma if the blood was stored as whole blood for a prolonged period and then separated into components immediately before administration. The leak of potassium from red blood cells is accelerated by storing the blood in cool temperatures and by irradiation. Risk factors for hyperkalemia in the neonate include the transfusion of old blood, cold blood, and irradiated blood, rapid and/or massive transfusion, hypocalcemia, renal dysfunction, and transfusion through central venous access [48, 145–147]. Washing the blood can minimize transfusion-induced hyperkalemia and the associated cardiac arrhythmias, particularly if the blood has been stored for a prolonged period. However, the greater the interval between washing and administering the RBCs, the more potassium will leak out of the cells. Rapid administration of cold, hyperkalemic red blood cells through a central line directly into the right atrium may cause the atrium to become irritable and trigger atrial and then ventricular arrhythmias or cardiac arrest [48]. To preclude such devastating complications, blood products should be warmed before transfusion to prevent hypothermia, and they should be infused through a peripheral IV line to prevent the associated dysrhythmias. Ideally, fresh units of blood and blood that has been stored for the briefest time since irradiation should be given to neonates to minimize the concentration of potassium in the cell-free fraction of the red cells. Other strategies include monitoring and maintaining ionized calcium blood concentrations within a normal range [145, 146].

Citrate is used as an anticoagulant in most transfused products, binding calcium and magnesium. Frozen plasma, whole blood, and platelets have the greatest quantities of citrate followed by red blood cell units and cryoprecipitate. Washing the units of red blood cells dramatically reduces the concentration of citrate in the acellular fraction. The metabolism of citrate (in the liver) is diminished in neonates, rendering neonates prone to the prolonged effects of circulating citrate compared with older children and adults [145]. Clinically, the rapid administration of citrate-containing blood products binds ionized calcium and causes bradycardia and hypotension that are magnified in the neonatal myocardium (see Chap. 2, Physiology and Development of the Term and Preterm Neonate). Hence, citrate-containing plasma should be infused at rates <1 mL/kg/min along with concomitant administration of calcium to maintain normal plasma calcium concentrations [145]. Exposure to large volumes of citrate through a massive transfusion may also lead to metabolic alkalosis as the citrate is metabolized in the liver.

Blood transfusions in neonates lead to both beneficial and pathologic associations that are poorly understood. In a large series of VLBW neonates, the mortality in those who received >1 blood transfusion increased, although the factors that were responsible for the increased mortality remained elusive [148]. The possibility of transfusion-associated NEC and BPD in VLBW infants has been described, but the pathogenesis is

poorly understood [149, 150]. An important outstanding question that remains unanswered is whether enteral feeds at the time of blood transfusions predispose to transfusion-associated NEC [150, 151]. In the absence of randomized controlled studies, a Cochrane review could not determine whether halting enteral feeds at the time of transfusion affected the frequency of NEC or death [152]. Nonetheless, red blood cell transfusion in extremely low-birth-weight (ELBW) infants (birth weight < 1000 g) may be a risk factor for ROP as well as untoward effects on late neurodevelopment, suggesting caution when choosing an appropriate transfusion threshold in this population [153]. Transfusion practices vary widely due to the lack of any consensus on the thresholds to transfuse [154]. More restrictive transfusion practices may result in a decreased incidence of associated morbidities of prematurity, but the evidence is still emerging [135, 155–157]. The results of the first of two large trials to address this complex topic [157] have been published. The results of the ETTNO (Effects of Transfusion Thresholds on Neurocognitive Outcome of extremely low-birth-weight infants) trial which included 1013 VLBW infants almost equally between liberal and restrictive transfusion strategies revealed no difference in mortality or disability (cognitive impairment or cerebral palsy) at 24 months after birth [156]. The results of the second trial, the TOP (Transfusion Of Prematures: NCT01702805) trial, are pending [157].

Transfusion-related acute lung injury (TRALI) and transfusion-associated circulatory overload (TACO) may be underdiagnosed in neonates, particularly in those with preexisting developmental lung disease [154, 158]. TRALI presents as the sudden onset hypoxemic respiratory failure within 6 h of transfusion, associated with non-cardiogenic pulmonary edema and bilateral lung infiltrates. Although life-threatening TRALI has rarely been observed in neonates, it should be considered in the clinical setting of a sudden deterioration in pulmonary function after blood component transfusion [159, 160]. A less well-known transfusion-related morbidity is transfusion-related immunomodulation (TRIM), which is a new area of transfusion research seeking to understand how blood products modulate immune cell function in neonates [159].

The indications to transfuse fresh frozen plasma (FFP) in neonates are variable as common laboratory studies are poor metrics of potential clinical issues in neonates. Neonates have a different balance of coagulation factors compared with older children, which still results in adequate global hemostasis despite laboratory abnormalities [161–163]. The transfusion of FFP in neonates should be clinically based, targeting evidence of bleeding rather than as a theoretic or prophylactic measure, except in cases of large volume blood loss [134]. In contrast, the transfusion of cryoprecipitate should be based on laboratory measures of the fibrinogen concentration if massive blood loss is anticipated.

In stable, non-bleeding, preterm neonates, reduced concentrations of platelets have been accepted as safe for surgery, thus reducing the need for platelet transfusions [134]. In a randomized trial of preterm infants with thrombocytopenia in the NICU, the use of a platelet transfusion threshold of 50,000 per microliter was associated with a greater risk of mortality or severe bleeding within 28 days compared with a reduced transfusion threshold of 25,000 per cubic millimeter [164], although the generalizability of this finding to surgical neonates remains unstudied. The presence of major hemorrhage in preterm infants is not primarily associated with the severity of thrombocytopenia [165].

Thromboelastographic (TEG) and thromboelastometry (TEM) are potentially useful tests of coagulation that reflect multiple factors involved in hemostasis, including fibrinolysis. Such viscoelastic tests can provide more information about the functional status of platelets as well as other components of the coagulation process even in preterm neonates [163]. The greatest experience with neonatal TEG has been in infants undergoing cardiopulmonary bypass or receiving extracorporeal membrane oxygenation (ECMO), but further evaluation of incorporating viscoelastic tests in transfusion algorithms is ongoing [166].

Vascular Access

Reliable vascular access is vital to the management of critically ill neonates but can also be a significant challenge to obtain, secure, and maintain. Vascular access is associated with a wide variety of complications and requires constant surveillance to diagnose and minimize the potential for harm. Common issues with vascular access include infections, disconnections, phlebitis, and extravasations. Extravasations can lead to significant complications including tissue necrosis and compartment syndrome. Less common complications include nerve damage, thrombosis, and embolism. Arterial lines have the added concerns of ischemic injury, formation of an arteriovenous fistula, and inadvertent injection of IV drugs [167]. Proper labeling of lines and access ports should minimize the chance of intra-arterial administration of a medication.

Neonates are at particularly high risk for vascular access-related complications. During the perioperative period, the incidence of thrombophlebitis and adverse events after arterial line cannulation in neonates was 185 and 148 per 10,000, respectively, whereas the incidence in infants, the group closest to neonates for these complications, was 20 and 49 per 10,000 respectively [9]. Studies that investigated the timing of replacing peripheral IV catheters favor clinically based algorithms rather than routine, timed replacement, which have been associated with increasing costs without decreasing adverse events [168–170].

Central venous access is essential for many critically ill neonates while introducing a wide range of potential complications [171–173] (see Chap. 7, Monitoring). Analysis of children with heart disease published from the POCA registry showed that central venous catheters were most frequently associated with equipment-related arrests, and 78% of arrests that were attributed to central venous catheters occurred in neonates [25]. Ultrasound is commonly used to increase the rate for the successful placement of central venous catheters as well as to confirm the location of the catheter tip [174–176]. Ultrasound can also assist in rapidly diagnosing catheter complications. Large vessel or right atrial perforation may occur either during attempts to place a central venous catheter or after it is placed due to erosion through the wall of the atrium. Emergent and potentially life-threatening conditions associated with central venous catheters include pneumothorax, hemothorax, and cardiac tamponade. These must be considered in any neonate with a central venous catheter who suddenly develops cardiopulmonary instability. Other complications include thrombosis (vessel and/or line), embolism, infection, hydrothorax, chylothorax, and unplanned displacement. In a retrospective review of 587 central venous catheters in neonates and infants, the complication rate was 28% (dislodgement 12%, perforation 5%, obstruction 5%, infection 4%, thrombosis 1%), with two deaths due to cardiac tamponade [177].

The combination of an underdeveloped coagulation system and small-caliber vessels containing a proportionately larger access catheter in the setting of an underlying critical illness predisposes the neonate to thromboembolic events. A Canadian, multi-institutional registry reported that even though thrombosis occurred infrequently in 97 neonates over more than 3 years from 64 centers, it was strongly associated with indwelling catheters (89%) and/or the presence of a systemic infection (29%) [178]. The registry also concluded that the greatest mortality occurred in neonates with an aortic, right atrial, or SVC thrombosis. In neonates who were scheduled for or undergoing cardiac surgery, the incidence of central venous line thrombosis was 3 to 10% [179, 180].

In addition to the common complications associated with chronic indwelling vascular catheters such as infection and thrombosis [181, 182], peripherally inserted central catheters (PICC) introduce a greater risk of rupture and potential embolization of a catheter fragment. In a series of 1650 PICCs, 11 fractures (0.67%) occurred, requiring invasive retrieval of fragments via a percutaneous intravascular approach [183]. Several factors were associated with catheter fracture including the duration of its placement, line occlusion, and leaking at the insertion site. Unless otherwise stated by the manufacturer, syringes ≥10 mL are recommended for injections into PICC to preclude excessive intraluminal pressure.

Oxygen Toxicity

The relationship between oxygen therapy and organ injury in preterm neonates and infants has been well-known for decades. Exposure to increased concentrations of oxygen in the first few weeks after birth is associated with an increase in the risk of ROP and BPD [184–186]. Efforts to reduce these sequelae in preterm infants born at ≤28 weeks' gestation led to several studies that examined the impact of a range of oxygen saturation targets on neonatal outcomes. Initial reports indicated that a reduced oxygen saturation target (85–89%) was associated with fewer sequelae of oxygen toxicity in survivors [181, 182, 187–190]. However, in 2016, the UK and Australian Benefits of Oxygen Saturation Targeting (BOOST)–II trials (BOOST-II) reported that this reduced target oxygen saturation range of 85–89% was associated with a significantly increased incidence of the combined outcomes of death and disability at a corrected gestational age of 18–24 months, and of dying alone, in post hoc combined analyses compared with the greater oxygen saturation range of 91–95% [191]. The Neonatal Oxygen Prospective Meta-analysis (NeOProM) Collaboration was comprised of five international, comparative effectiveness trials and included the two trials from BOOST–II to further evaluate the impact of these two oxygen saturation ranges [188, 191–193]. NeOProM analyzed almost 5000 neonates in two prospectively planned publications that concluded there was no overall difference in the primary composite outcome of major disability or death in those treated with the reduced (85–89%) versus greater (91–95%) oxygen saturation target range by a corrected age of 24 months [192, 193]. However, the reduced oxygen saturation range (85–89%) was associated with a significantly greater incidence in the secondary outcomes of mortality by 18–24 months, death before hospital discharge, NEC, and patent ductus arteriosus that required surgical ligation while significantly reducing the incidence of ROP and BPD. The net result is that the optimal target oxygen saturation for preterms infants in the NICU remains unclear with many outstanding questions [194, 195]. In the future, advancing technologies such as closed-loop, automated oxygen control may prove effective in maintaining more consistent target oxygen saturations and identifying the optimal target oxygen saturation in these neonates [196–198] (see Chap. 2).

When anesthetizing preterm neonates for surgery, anesthesiologists strive to avoid the extremes of hypoxia and hyperoxia to minimize the contributions of either insufficient or excessive oxygen exposure to adverse sequelae, even after a brief exposure. We advocate a multidisciplinary discussion to determine the acceptable peri-anesthetic target oxygen saturation or range of saturation together with the minimum inspired concentration of oxygen to achieve this goal. In the

absence of confounding variables, the authors and the editor recommend that the inspired oxygen fraction be adjusted to achieve a midrange oxygen saturation of 90–92% during anesthesia in preterm neonates. Even though a precise target saturation is not supported by the current evidence, we can state categorically that an oxygen saturation of 100% is not only unnecessary but is potentially harmful, especially if it requires a large fraction of inspired oxygen to achieve.

Concerns related to the impact of oxidative stresses in neonates have led to changes in delivery room resuscitation guidelines. Two meta-analyses of randomized, controlled trials that compared the initial resuscitation with 100% oxygen with room air resuscitation showed greater survival with room air [199, 200]. However, the methodologies used in these studies have been criticized, leading to much weaker evidence of the benefit of reduced oxygen concentrations for resuscitation of the neonate [201]. In the case of the preterm neonate, best practice and neonatal resuscitation program (NRP) guidelines currently suggest using a FiO_2 of 0.21–0.30 to initially resuscitate these neonates and titrate the FiO_2 thereafter to achieve age-appropriate oxygen saturation targets [202]. If the bradycardia persists after ventilation with room air, then the neonate should be administered increasing concentrations of oxygen up to 100% [203, 204].

Although there is no consensus on the ideal oxygen concentration for use during neonatal anesthesia, preventing hypoxemia is an indisputable goal for every pediatric anesthesiologist. We also recommend avoiding hyperoxia to minimize the risks of adverse effects [205–207] (see Chap. 2)

Prevention of Adverse Events

Human Factors

The human dynamic in adverse events plays a significant role in patient safety in the peri-anesthetic period. As stated by Allnutt [208]:

> …all human beings, without any exception whatsoever, make errors and that such errors are completely normal and necessary part of human cognitive function. For a … doctor to accept that he or she is as likely as anyone else to make a catastrophic error today is the first step towards prevention; whereas to claim exemption on the grounds of being a … senior professor, … or consultant [attending]…, is the first step on the road to disaster.

The Institute of Medicine publications *To Err Is Human* and *Crossing the Quality Chasm* identified the annual cost of more than 40,000 lives and 2 billion dollars lost by the US healthcare system due to failures of safety and quality [209, 210]. This information has prompted dramatic quality improvement initiatives, including in the practice of pediatric anesthesiology [211]. Over 30 years ago, the 1989 National Confidential Enquiry into Perioperative Deaths emphasized three ideals [212, 213]:

1. Surgeons and anesthesiologists should not undertake occasional pediatric practice.
2. Anesthesiologists who care for children must keep themselves up to date and competent in pediatric anesthesia.
3. Consultant supervision of trainees needs to be kept under scrutiny.

These recommendations promoted the concept of regionalization for pediatric and, in particular, neonatal surgical care in the United Kingdom [213]. The United States does not have any formal system of regionalization despite the clustering of pediatric institutions staffed with pediatric subspecialists [214, 215]. Increased volume of cases, specialty-specific training and experience, and triaging high-risk and rare cases to specialty centers are additional strategies that decrease the risk and human error [12, 13, 215–221].

Emphasizing the importance of continuous, competent practice in the preterm and term neonates, evidence suggests that many modifiable perioperative factors may contribute synergistically to neonatal neurological injury. Systemic hypotension or hypertension outside the autoregulatory range, hypocapnia, hypercapnia, increased intracranial pressure, or obstructed central venous drainage may adversely affect cerebral perfusion. Neuronal cell death may also be promoted by insufficient metabolic or oxidative fuel, such as hypoglycemia or hypoxia, especially in times of increased demand during hypermetabolic states such as pain, fever, seizures, or other physiologic stressors. Neurotoxic mediators may also cause brain injury from the sequence of hypoxia and ischemia, followed by reperfusion and free radical oxidative stress from hyperoxia [222].

A retrospective analysis from a single pediatric institution investigated the role of human factors in 668 reported anesthetic incidents, representing 2.4% of the total anesthetics provided. The analysis concluded that human factors accounted for 284 (42.5%) of the incidents with the two most common errors being judgment and failure to check equipment, tracheal tubes, and lines [18].

The following processes decreased severe critical incidents of death and coma in a large, multicenter adult population [223]; their implementation would be expected to have a similar impact on safety in neonates:

1. Routine use of an equipment protocol and checklist.
2. Availability of an anesthesiologist for additional help and insight.
3. Use of full-time anesthesia team members.
4. Presence of two anesthesia team members at emergence and transfer.

5. Reversal of muscle relaxants at the end of an anesthetic before extubation.

In addition to checklists, targeted feedback and updating protocols decrease the role of human factors in adverse events [18]. Recognizing that anesthesia provider who is distracted is a patient safety hazard, a 2017 process improvement project implemented at the Vanderbilt University Medical Center decreased environmental distractions such as music, loud noises, and unnecessary conversation during induction of anesthesia in pediatric otolaryngology ORs from 61% to 10% [224].

Medication Errors

Human factors play a pivotal role in medication errors. Medication errors are among the most frequent critical event in anesthesia and are underreported [225–230]. Anesthesia providers are unique in terms of managing medications, prescribing, identifying, dispensing, calculating, diluting, programing, administering, and recording the drugs given, most often without verification by other personnel. Drug calculation errors have been reported by staff and resident anesthesiologists [231–233]. The incidence of drug errors in anesthesia is 1–5%, with untoward outcomes reported including death [226, 231]. In 2010, the Anesthesia Patient Safety Foundation convened a summit that produced a new paradigm of standardization, technology, pharmacy/prefilled/premixed, and culture to reduce drug errors in the OR area [231].

Despite recent advancements in neonatal pharmacokinetics, pharmacodynamics, and clinical outcome measures, significant knowledge gaps persist [234–238]. Neonatal dosing requires dose calculation and administration of drugs from concentrations and volumes that are generally manufactured for adults. Developmentally immature organ and metabolic processes in the neonate, amplified in the preterm neonate, together with the lack of methods to measure medication effects quickly and reliably, contribute to the complexity of determining appropriate doses and dose frequency. A variety of disease states further alter metabolism during complex and high-risk procedures that demand rapid decision-making and intervention.

Research indicates that medication errors as a percentage of incidents in pediatric anesthesia have remained relatively unchanged over the last three decades (~2% to 6%) [9, 15, 17, 18, 20, 24, 239]. Prior reviews of critical incidents in pediatric anesthetic demonstrated that medication errors accounted for 4.4% of all errors, with anaphylaxis as the most common event in this category [15]. In contrast, a review of critical incidents in children during the extended perioperative period reported to the UK National Reporting and Learning System over 3 years revealed that medication issues predominated at 35.6%, nearly double the next closest category, airway, and respiration at 18.8% [111]. The majority of these were administration errors, including unintended additional dosing in which an anesthesiologist was one of the healthcare professionals involved but may not have made the error. As this review included the hospital course, a greater overall percentage of medication errors points to increased concerns for appropriate perioperative communication between healthcare providers during the transition from the OR to the postanesthesia care unit and intensive care unit.

A 2016 review of the Wake Up Safe database revealed that medication errors were the third most frequent category of events only behind cardiac- and respiratory-related events. Errors during administration accounted for 65% of medication errors, and nearly 31% of the errors were due to administration of the wrong dose, followed by an accidental syringe swap in 18%. Over 80% of the errors were conveyed to the patients, and more than 50% caused harm with 5% of the patients requiring a life-sustaining intervention. The review determined that 97% of errors were likely or certainly preventable [240].

In 2017, the Pediatric Anesthesia Trainee Research Network conducted a survey of 162 anesthesia trainees and staff, of whom 60% described they made pediatric drug errors at least once a year and 15% reported an error at least once a month [229]. Of those surveyed, 36% stated that they would only report drug errors if they resulted in patient harm, which limits individual and systemic education from unreported near-miss events. Drug calculation and dilution errors constituted half of all reported errors, while 16% resulted from failure to flush the intravenous catheter, and 11% were due to administering the wrong drug. Evaluation of drug dilution performed by pediatric anesthesiologists revealed that irrespective of the practitioner's experience, the measured drug concentration is in error by >10% from the targeted concentration in 70% of the samples and > n 30% off the target in 23% of the samples [241]. These data support the use of standardized, prefilled syringes for neonates, infants, and children.

A single-institution, retrospective study showed the rate of medication errors in pediatric anesthesia started at 7 per 10,000 cases and then, after implementing a series of interventions to decrease drug errors, decreased to 1.7 per 10,000 over 8 years [242]. In a prospective study from a single institution that captured data from 73% of its cases over 3 months, the authors reported a medication error rate of 264 per 10,000 cases [243]. The results of a meta-analysis of medication errors in pediatric anesthesia yielded an error rate of 8 per 10,000 cases, a rate that was much less than the published data from adults, approximately 75 per 10,000 cases. As a

result, the authors expressed concern about the validity of the published research methods and the reliance on self-reporting of drug errors in pediatric anesthesia [244].

Few studies have addressed the risks of medication errors specifically in neonates; however, the consequence of adverse drug events may be significantly greater in neonates than older children [245]. In both neonates and children, the incidence of drug errors is similar; however, the risk of a 10- to 300-fold error has led to serious or potentially serious adverse sequelae, which is particularly concerning given that many drugs administered to neonates are off-label and incompletely studied [238, 246, 247]. Adverse and potential drug events in the NICU as part of a larger study in a university-affiliated pediatric occurred in 19 and 27 per 1000 hospital days, respectively, of which 14 adverse drug events per 1000 hospital days were deemed preventable. Interestingly, the frequency of adverse drug events in the NICU was less than the average for all hospital areas studied, with the pediatric surgical ward leading with the most events, 65 per 1000 hospital days [248]. In contrast, another study reported that neonates in the NICU had the greatest risk of calculation errors compared with older children [245]. A recent review of medication errors and adverse events in the NICU showed that error rates varied from 4 to 35 per 1000 patient-days and from 6 to 78 per 100 medication orders with prescribing and medication administration errors as the most common medication errors and dosing errors the most frequently reported error subtype [249]. This study reported preventable adverse drug event rates were 0.9 per 1000 doses and 0.5–14 per 1000 patient-days in NICUs.

The technique of administering bolus and continuous IV medications plays a central role in neonatal care. Undiluted or minimally diluted formulations of bolus medications result in small administration volumes (tenths of a milliliter), which can be easily lost or captured in the dead space of IV tubing, syringes, and access ports, significantly delaying or decreasing the intended drug effect. This can also lead to accidental dose stacking with risk for ensuing complications. The administration of extra or even excessive volume may occur when more diluted infusions are used or with the need for repeated medication flushes [250, 251]. Only preservative-free flush solutions should be used for neonates to prevent the excessive accumulation of potentially toxic preservatives such as benzyl alcohol [250, 252]. The setup of the IV and infusion lines together with the drug concentration and flow rates plays an important role in the lag time to achieve steady-state blood concentrations of the drug and in the amount of drug in the system architecture that may be available for an inadvertent bolus [251].

Systematic countermeasures should aim to decrease the number of drug administration errors in anesthesia. The "six rights" of medication administration to avoid errors are verifying the correct patient, dose, medication, time, route, and record (i.e., documentation of the medication administered and wasted) [255]. In addition to these "rights," additional systems must be designed and implemented to further diminish the chance of an error occurring. Methods to decrease medication-related errors can include stringent drug labeling on syringes and vials, barcoding all vials, color-coding by class of drugs, removing dangerous drugs from "open" anesthesia carts and drawers, and not storing similar appearing drug containers near each other [15, 53, 256]. Table 17.1 includes strategies to decrease the risk of medication errors in anesthesia, some of which are directed toward the individual practitioner since no system completely eliminates medications errors [255]. In 2017, Seattle Children's Hospital instituted a project to reduce medication errors [253] in which they identified 5 targeted countermeasures that decreased the error rate from 1.56 to 0.95 per 1000 anesthetics: medication tray reorganization, medication top cart template, syringe labeling, infusion double-check, and medication practice guideline posted in every room.

Table 17.1 Strategies to decrease medication errors

Labels
Similar packaging and presentation of medications should be avoided where possible.
The legibility and contents of labels on ampules and syringes should be optimized according to agreed standards.
The label on any drug ampule or syringe should be read carefully before a drug is drawn up or injected.
Syringes should always be labeled.
Organization
Medication drawers and workspace should be formally organized into a known and consistent template.
Any changes in presentation should be notified ahead of time.
Potentially hazardous medications (e.g., concentrated epinephrine, concentrated phenylephrine, insulin, bupivacaine) should be separated, either visibly with specific colors or another identifier or spatially from those that are routinely used.
Strongly consider designating a pharmacist to the operating theaters.
Calculations
Reduce calculation errors by accessing weight-based references, and integrate systems that provide such support.
Resources need to be allocated to employ prefilled syringes in the appropriate concentrations for neonates rather than individuals diluting concentrated medications.
Independent double-checks
Labels should be checked with a second person or with a device (such as a barcode reader linked to a computer) *before* any medication is prepared or administered.
Medication infusions require a second individual to verify concentration and dose.
Reporting
Errors in intravenous drug administration during anesthesia should be reported and regularly reviewed to identify areas for improvement, both individual and systemic.

Adapted from the following references: [226, 228, 240, 253–255]

Another key strategy to prevent drug errors is to add multiple barriers to the error pathway such as standardized concentrations for continuous infusions, standardized packaging of pediatric medications rather than relying on adult formulations, prefilled syringes, use of barcodes to verify medications before their administration, and reengineering drug delivery systems such that intravenous, intra-arterial, and regional syringes or infusion lines cannot be interchanged [53, 256, 257]. Ready-to-administer products such as prefilled syringes have been found in a recent study to be associated with significantly fewer errors than traditional IV injection practices [258]. Barcode assisted labeling systems have improved medication safety in the ORs [259], emergency departments [260], and inpatient units [261–263], although further study in the OR environment is warranted. As with most solutions to complex problems, these steps are likely to add extra costs while still requiring the provider to remain fully engaged and diligent.

In 2014, an observational, single-institution study on weight-based infusion calculations in children reported that only 15% of the written responses were error-free and the observed mean time for the calculation exceeded 3.5 min [264]. The calculations ranged from 50 times too small to 56 times too large of the correct dose. In 2019, a study involving seven academic training institutions in the United States explored computational drug error rates by anesthesiology residents and faculty by administering a written test. They identified a mean error rate of 17%, with the more junior residents and more experienced faculty both making more frequent errors, with the magnitude of the residents' errors more extreme than the other groups. Only 20% of residents and 25% of faculty correctly answered all of the questions [233].

Considering the narrow therapeutic index of many anesthetic drugs, the occasional 10-fold to 1000-fold computational errors observed in this study suggest the need for a process improvement initiative to decrease this risk. Suggested mechanisms have included didactic sessions and testing in computational competency as core requirements for anesthesiology residents [265]. A study of 277 anesthetic cases at the Massachusetts General Hospital reported a drug error or adverse drug event rate of 1 in 20 medications administered [226]. The most common type of error identified was improper drug labeling. The event rate across house staff, CRNAs, and attending anesthesiologists did not differ significantly, which suggests that these errors are not simply attributable to a lack of experience or to distracted care providers. These data support the exploration of technologies designed to enhance safety in the OR, where redundant, multiple checks before drugs are administered remain an uncommon practice. An analysis of allowing overrides of medication-related decision support alerts revealed that clinicians override most alerts, resulting in inappropriate overrides 40% of the time, although more than 75% of the overrides on warnings of significant harm were inappropriate [266].

Despite decades of recognizing drug errors in anesthesia as a substantial patient safety issue, there has been insufficient progress in reducing medication errors and insufficient, robust studies to uncover the complex mechanisms involved and the potential solutions. When institutions, industry, and regulatory agencies mandate that the formulation, distribution, and administration of pediatric and neonatal medications are standardized, and clinicians are given support to implement the updated, standardized systems at the bedside, only then will adverse drug events finally be harnessed and substantially reduced.

Equipment-Related Incidents

Equipment-related incidents in pediatric anesthesia contribute a small but important role in adverse or "near-miss" events. Comparing the outcomes from studies is difficult because some only report critical events and others report both critical and potentially critical events. The actual definition of equipment-related incidents is not always stated or consistent among the studies. Pediatric closed claims cases in the United States [10] and the Australian Incident Monitoring Study [11] reported that equipment-related events comprised 13% and 14% of total claims or incidents, respectively. In a more recent pediatric closed claims analysis, equipment-related issues were cited in 15% of claims [22]. Data from the POCA registry from 1994 to 1997 and 1998 to 2004 reported equipment-related events in 7% and 5% of total events, respectively, with central venous catheter complications the most frequent complications followed by problems with the tracheal tube or breathing circuit [13, 19]. The POCA registry also reported the rate of equipment-related arrests as 9% in children with congenital heart disease [25]. A review of critical incidents affecting or potentially affecting the perioperative anesthetic management in children under 16 years of age reported to the UK National Reporting and Learning System from 2006 to 2008 showed equipment-related incidents to be 15.7% of the total without any associated deaths or reports of severe harm [111]. As this review included potential harm, the greater rate is not surprising even though venous access complications were not included in the equipment category. Equipment-related events in institutional or multi-institutional studies ranged from approximately 1% to 10% of total events reported [8, 15, 17, 18, 20, 43]. Most of these involved the anesthesia machine or the breathing circuit and tracheal tube.

Addressing Risks and Adverse Events

Ideally, reconstructing the course that led to a critical incident such as with a root cause analysis may provide a broader overview of the processes that combined to result in an adverse event. Prospective collection of such information for adverse events is essential yet exceedingly difficult, particularly for rare events. Analysis of the contributing factors should then lead to strategies and tactics to manage and control potential safety threats, to improve safety and outcome. As neonates are a high-risk anesthetic population and are at greater risk for perioperative complications [53], both institutional and individual stakeholders must focus on identifying the root causes of adverse events and developing outcomes research to appropriately implement or modify processes to prevent or reduce their occurrence [53]. Stakeholders must also critically review findings to appropriately address patient safety during anesthesia, which may require implementing new strategies or redeploying resources [219, 223].

Optimizing patient care by verifying anesthetic equipment and medications with appropriate dilutions, labels, and double-checks before induction is essential and should be routine. Setting parameter limits and appropriate alarms is vital in such a complex environment. As anesthesia information systems, monitors, machines, and equipment advance in capacity and integration, preset alarm limits based on the age of the child and adjusted for various periods of an anesthetic could be tied to an anesthesia information management system such that as the case progresses from induction to emergence, so do appropriate alarms settings. Concerning alarms can also be forwarded to all providers covering the case via the institution's integrated communication system to alert those not at the bedside.

Asking for help, either by a consultation with another pediatric anesthesiologist or having an extra team member present when needed, is an excellent strategy to decrease adverse events [223]. Providers who are specifically trained for and experienced in high-risk subpopulations can decrease the risk of adverse events [12, 215–217, 219, 221, 267, 268]. This holds true for all areas of care, from the preoperative to the postoperative setting. Practitioners must engage in self-reflection and seek feedback. Institutions and departments must provide mechanisms and processes for feedback such that the appropriate steps may be taken to understand and prevent further mishaps. Continuing medical education and implementing evidence-based practices are essential to maintain skills and provide safe, appropriate care, for example, by incorporating the Enhanced Recovery After Surgery guideline for surgical neonates which included 17 recommendations developed by an international team using a rigorous, evidence-based, consensus-driven process [269].

The Task Force for Children's Surgical Care convened its first meeting in May 2012, originally with representatives from several pediatric surgical disciplines and the Society for Pediatric Anesthesia. It was subsequently expanded to include additional representatives from the full array of pediatric surgical specialties as well as neonatology, pediatric radiology, pediatric critical care, and pediatric emergency medicine. The task force produced a white paper [270] and consensus statement [215] which stated that neonates are a pediatric subpopulation with differential outcomes in specialized versus nonspecialized surgical environments. The task force unveiled the Children's Surgery Verification program in January 2017 with the intent of establishing multidisciplinary standards for pediatric perioperative care [267]. Hospitals applying for verification are designated as Level I, II, or III based on resource allocation, such as the on-site presence of pediatric anesthesiologists and other pediatric surgical and medical subspecialists. The American Society of Anesthesiologists has expressed concern that this program may have the unintended consequence of reduced access to care and increased burdens on families, particularly in rural areas [271]. The Global Initiative for Children's Surgery was formed to help low- and middle-income countries to develop and implement regional- and national-based standards in an attempt to optimize care for pediatric surgical patients, which also will improve surgical and anesthetic care for neonates globally [272, 273].

Although medical errors are classically associated only with patient harm, a spectrum of consequences may occur with a medical error ranging from tangible harm to real benefit. Many medical errors have no positive or negative patient impact and might be referred to as a near miss, whereas a smaller yet not insignificant number have important consequences. In an unplanned extubation after a surgical procedure, wherein the patient remains safely extubated, the patient may indeed benefit from both the medical errors of planning, i.e., inappropriate continuation of mechanical ventilation, and execution, i.e., unplanned extubation. Learning from the unexpected and even beneficial consequences of medical error may improve the quality of care and aid in redefining optimal care [274].

Incident reporting systems are patient safety mechanisms that are capable of identifying risks and improvement opportunities. While they can be a valuable tool for gathering incident data, underreporting remains a major limitation likely due to barriers such as concern for punitive repercussions, feelings of incompetence, insufficient understanding regarding what constitutes an event, lack of feedback, and the perception of irrelevance of reporting. An analysis of perioperative adverse events reported by pediatric anesthesiologists determined that these barriers were optimally addressed through education, encouraging reporting as part

of a culture of safety, feedback from those reporting, and increasing the involvement of anesthesiologists in patient safety initiatives [239]. Clinical outcomes research must proceed with the goal of identifying common parameters to measure, maintaining universal definitions for parameters and their assessment, and aggregating data from multiple sources to better assess both the more common minor adverse events and the rare yet potentially devastating major events. Many organizations are advancing this ideal including the Society for Pediatric Anesthesia, through its support of various safety registries and collaboratives (Table 17.2).

WUS member institutions apply a root cause analysis model to serious safety events that result in moderate to severe patient harm, precursor safety events that reach the patient but result in minimal or no detectable harm, as well as near-miss safety events that do not reach the patient [278]. The goals are to identify how the event occurred (active error) and why the event occurred (latent error) and then to prevent future errors. Recognizing that errors often result from the interaction between humans and complex systems, Wake Up Safe aims to improve the quality of delivered care by designing safer systems. The database resulting from this process has already led to published advisories regarding wrong-site procedures, medication errors, and cardiac arrest associated with blood transfusion in young children [47].

Table 17.2 Selected organizations dedicated to improving the anesthetic care of pediatric patients

Society for Pediatric Anesthesia (SPA)
https://www.pedsanesthesia.org/
Sections
Congenital Cardiac Anesthesia Society (CCAS) – ccasociety.org
Pediatric Regional Anesthesia Network (PRAN) [275]: pranetwork.org
Society for Pediatric Pain Medicine (SPPM): pedspainmedicine.org
Wake Up Safe [45, 47, 49, 118, 240, 276]: wakeupsafe.org
SPA Pedi Crisis Critical Events Checklist (SPA Quality & Safety Committee) [277]: https://www.pedsanesthesia.org/critical-events-checklist/
Special Interest Groups
Biomedical Informatics & Technology
Pediatric Craniofacial Collaborative Group (PCCG) [139, 142–144]
Pediatric Critical Care Medicine
Pediatric Difficult Intubation Collaborative (PeDI Registry) [41]
Pediatric Liver and Intestinal Transplant (PLIT)
Pediatric Perioperative Surgical Home
Simulation
Task Force for Children's Surgical Care
Children's Surgery Verification (CSV) Quality Improvement Program
https://www.facs.org/quality-programs/childrens-surgery/childrens-surgery-verification
Optimal Resources for Children's Surgical Care
International Anesthesia Research Society
Smart Tots: https://smarttots.org/
American Society of Anesthesiologists
Anesthesia Quality Institute: https://www.aqihq.org/introduction-to-nacor.aspx
American Academy of Pediatrics
Section on Anesthesiology and Pain Medicine: https://services.aap.org/en/community/aap-sections/anesthesiology-and-pain-medicine/

As pediatric anesthesiology designs, studies, and implements high-reliability science to move toward reducing error rates, simulation is playing a prominent role [279–284]. Simulation can provide an excellent learning environment without putting patients at risk. Simulations can help teams prepare for events, practice new models of care, as well as uncover and address individual, team, and system vulnerabilities.

Helping practitioners avoid cognitive errors is essential to avoid errors during patient care [285]. Cognitive aids provide benefit in ORs for routine processes including the presurgical time-out such that there are reasons to anticipate their benefit during critical events [286]. Checklists increase both the accuracy and speed of responses during critical events that may otherwise be limited by cognitive-processing limitations and confusion [287, 288]. A study on the implementation of an emergency manual conducted from 2013 to 2016 at a large academic anesthesia practice found that anesthesiology attending physicians, resident physicians, CRNAs, and SRNAs using their institution's customized version of the Stanford Emergency Manual consistently performed better in the verbalization of critical actions during simulated crisis events [289]. However, a review of anesthesia-specific checklist found them limited and heterogeneous [288]. To address the need for cognitive aids, the Quality and Safety Committee of the Society for Pediatric Anesthesia developed the SPA Critical Event Checklists (SPA-CECs) [290].

The evolving field of clinical genomics is expected to improve the diagnosis of and care for critically ill children including neonates as many may have undiagnosed, underlying genetic conditions [291, 292]. The Australian Genomics Acute Care Study showed the feasibility and blueprint of implementing ultrarapid genomic testing in critically ill infants and children of which 57% were from NICUs [293]. They found the ultrarapid genomic testing influenced the clinical management in 87% of tested patients. Hopefully, an improved ability to rapidly diagnose neonates with previously unconsidered genetic conditions will allow more targeted anesthetic and surgical care and decrease the potential for adverse events.

Adverse events must also be studied by utilizing multidisciplinary improvement measures that identify not only specialty-specific factors but also specialty-related and shared factors [214]. For any of these to be achievable, the development of uniform pediatric standards, central pediatric registries, appropriate benchmarks, and a robust infra-

structure must occur. To borrow from Peter Davis and the national security and intelligence communities, only then can we "move beyond the known knowns and known unknowns to the unknown unknowns" in pediatric as well as neonatal anesthesia [294].

Conclusion

The incidence of perioperative morbidity and mortality in pediatrics is greatest in neonates and decreases thereafter. That neonates are at greater risk for complications is not surprising as they often present for emergency surgery with complicated multiorgan disease, sepsis, and/or congenital heart disease. These coexisting disorders, along with organ immaturity as the neonate transitions from the fetal to the extrauterine environment, increase the perioperative risk. The complex environment and dynamics of a procedural area combined with the vulnerabilities of a high-risk population converge to increase the likelihood of adverse events occurring. The ultimate goal in developing and executing a successful anesthetic plan is to prevent adverse events, although a more realistic and achievable objective is to pursue strategies that decrease the number of adverse events and minimize their clinical consequences should they occur. Since peri-anesthetic systems require human interaction and decision-making, human errors are bound to occur. Continued improvements in perioperative and peri-anesthetic systems are essential to improve resiliency and decrease all types of errors. Continued, sustained improvements in safety and outcomes will be realized for our smallest and most vulnerable patients through ongoing data collection and analysis using globally agreed-upon terms and definitions, further standardization, continued education, innovative strategies, and persistent diligence in the peri-anesthetic period.

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Do Anesthetic Drugs Harm Neonates? A Global Perspective

18

Tom G. Hansen, Steen W. Henneberg, and Thomas Engelhardt

Introduction

There is still much to be discovered regarding how exposure to anesthesia affects the immature and developing brain. Given that the commonly used anesthetic agents exert their actions via N-methyl-D-aspartate (NMDA) and gamma-aminobutyric acid ($GABA_A$) receptors, it is biologically plausible that exposure during periods of vulnerable brain development may affect long-term outcomes (Table 18.1) [1, 2].

The provision of anesthesia for surgery in neonates and infants is a medical necessity. In addition to the humanitarian and ethical reasons to provide anesthesia, surgical and medical procedures should be performed safely and effectively, minimizing the stress of surgery [3]. However, numerous studies in newborn animals suggest that anesthetics lead to both short-term and long-term neurological changes [4, 5]. It is unclear whether this evidence translates in whole or in part to the human experience given the physiological and developmental differences between animals and humans. Studies of neurocognitive function in young children after anesthesia are emerging slowly, and the results from those studies demonstrate far less consistent and, in some instances, directly conflict with those in newborn animals. Translating the results of animal studies to the human clinical context is fraught with known pitfalls [6]. How do

Table 18.1 Receptor activity of commonly used anesthetic agents[a]

Anesthetic agent	NMDA antagonist	GABA-mimetic	μ-Opioid agonist
Volatile anesthetics			
Halothane	–/0	+++	0
Isoflurane	–/0	+++	0
Desflurane	–/0	+++	0
Enflurane	–/0	+++	0
Sevoflurane	–/0	+++	0
Injectable anesthetics			
Propofol	0	+++	0
Barbiturates	0	+++	0
Etomidate	0	+++	0
Benzodiazepines	0	+++	0
Ketamine	– – –	–/0	0
Medical gases			
Nitrous oxide	– – –	+++	0
Opioid analgesics			
Morphine	–/0	0	+++
Methadone	–	0	+++
Meperidine	–/0	0	+++
Fentanyl	–/0	0	+++
Other sedative hypnotics			
Chloral hydrate	– – –	+++	0
Trichloroethanol	– – –	+++	0
Ethanol	– – –	+++	0

Key: (– – –), strong antagonism within the clinically relevant range based on available in vitro data; (+++), strong potentiation within the clinically relevant range based on available in vitro data; (–/0), little antagonism within the clinically relevant range based on available in vitro data; (+/0), little potentiation within the clinically relevant range based on available in vitro data; (0), no compelling data to support activity at this site within the clinically relevant range

NMDA N-methyl-D-aspartate, *GABA* γ-aminobutyric acid

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[a]Receptor activity as noted in the table does not imply mechanisms of action; rather it indicates potential to neurological injury. The table was adapted, in large part, from reviews by Krasowski and Harrison (9) and by Dilger (10); for more detail, please refer review articles

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various stages of brain development in animal models translate into comparable stages in humans? Given the numbers of neonates, infants, and young children who are anesthetized annually, if the animal evidence of neurocognitive dysfunction also held for humans, then these data would have already had demonstrable and significant effects on infants and children together with widespread public health implications. The subject of anesthesia-induced neurotoxicity in neonates, infants, and children continues to come under increasing scrutiny by both healthcare providers and the public after recent public health announcements from the Food and Drug Administration (FDA) in the USA regarding the neurocognitive risks of anesthesia in infants and children including the parturient [7, 8].

The purpose of this chapter is to summarize the available scientific evidence regarding the effects of anesthetics on neurodevelopment in animals, summarize the current preclinical and clinical human data, highlight specific areas of concern in the clinical care we provide neonates and infants, and outline potential strategies that may minimize the potentially harmful effects of anesthetics on neonates and young children.

Animal and Preclinical Data

Brain development begins with the embryonic period, from conception until the eighth week of gestation [9]. At this time, the major structures that form the central and peripheral nervous systems are completed. From 8 weeks to the end of gestation, this period of rapid brain development witnesses the formation of cortical and subcortical structures complemented by cellular changes that create major fiber pathways. Gyri and sulci form in sequence between 8 and 22–26 weeks gestation. Brain growth continues throughout gestation and after birth, with the brain increasing fourfold in size during the preschool-age period, reaching 90% of adult size by 6 years of age. Throughout childhood and adolescence, both white and gray matter continue to develop. From the third trimester (27 weeks gestation) until 3 years of age, the period known as rapid synaptogenesis, extensive connections between neural cells explode with neuronal migration, synaptogenesis, and differentiation and maturation of the cells, all mediated by glutamate, the excitatory neurotransmitter. Both glutamate and GABA effect their actions in the nervous system via one of two receptors: ionotropic (ligand-gated ion channels) or metabotropic (G protein-coupled) receptors. Here we focus on the ionotropic receptors. The ionotropic glutamate receptors are named after their agonists: α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid, kainite, and NMDA (N-methyl-D-aspartate), the last forming three subunits, NR1, NR2, and NR3 [10–12]. The ionotropic GABA receptors are comprised of eight subtypes, with the $GABA_A$ receptors themselves comprised of three of their subtypes, α, β, and γ. Both NMDA and $GABA_A$ receptors are integrally involved in mediating the trophic factors that cause neuronal cell migration, differentiation, proliferation, and dendritic maturation during this period. During rapid synaptogenesis, the NMDA receptors are hypersensitive and if stimulated will trigger excitotoxic cell death. Additionally, they are indirectly involved in the modulating trophic factors that mediate programmed cell death or apoptosis, which is defined below. If during the same period the NMDA receptors are blocked, then apoptosis will be activated. As the nervous system develops, an abundance of neurons is formed. Those neurons that form functional synapses and integrate fully into the neural network survive, whereas those that fail in these respects are pruned by apoptosis [13]. As many as 50% of the cells in any one organ may undergo apoptosis during growth and development, although only 1% of the cells undergo apoptosis at any one time. Since most anesthetics either antagonize NMDA receptors or activate GABA-ergic receptors, the same receptors that mediate apoptosis, investigators discovered totally by serendipity that massive neuroapoptosis occurred in newborn rodents who were anesthetized for but a brief period, uncovering a potentially serious and previously unforeseen risk of neurocognitive dysfunction after anesthesia if the same held in humans. This discovery fostered an enormous number of investigations and funded research activity that explored the how, when, and why this occurs and its implications for humans. Below, we summarize those findings.

The biologic phenomenon known as physiological cell death follows one of two paths: necrotic or apoptotic [14, 15]. Necrotic or excitotoxic cell death usually follows a traumatic, toxic (drug-related), or inflammatory event that causes the affected cell to swell and rupture, releasing its cellular contents. The contents, which include inflammatory proteases and lysozymes, trigger an acute inflammatory process locally that causes characteristic edema, swelling, and inflammation well-known after head injuries. During the period of rapid synaptogenesis, this results from activation of NMDA receptors during the period of hypersensitivity. In contrast, programmed cell death or apoptosis is the orderly removal of ineffectual and redundant cells in an organ by phagocytosis, preventing the release of intracellular enzymes that might trigger an inflammatory response. Apoptosis is a normal process that occurs during organ development in all tissues including the brain. Central to distinguishing these two processes is the relative contributions of the NMDA and $GABA_A$ receptors. When NMDA receptors are stimulated or triggered during rapid synaptogenesis, a period of rapid growth of synapses in the brain results in excitotoxic cell death, whereas when these same receptors are blocked, they trigger apoptotic cell death [16]. This latter phenomenon was

elegantly simulated by administering the NMDA-receptor antagonist, MK-801, which like ketamine led to widespread neuronal apoptosis, exceeding the naturally occurring apoptosis by several orders of magnitude [1]. Additionally, investigators discovered that when $GABA_A$ receptors are activated, it also triggered neuronal apoptosis (Fig. 18.1).

The earliest animal studies that reported anesthesia-related neurotoxicity in the developing brain arose from neither clinical concerns nor anecdotal suspicions that general anesthesia impaired neurocognitive function in neonates. Anesthetic-induced neurotoxicity was discovered by serendipity during studies of fetal alcohol syndrome and neuronal injury after head trauma in newborn rats [17]. Alcohol ingested during pregnancy is known to injure the brain of the developing fetus proportional to both the amount of and frequency that alcohol is ingested, as well as the timing during pregnancy. Alcohol causes widespread apoptosis and neurocognitive dysfunction by inhibiting NMDA receptors and/or augmenting $GABA_A$-ergic activity. During the period of rapid synaptogenesis, synaptogenesis is rapid, and dendritic spin density increases, with both of these processes depending on these two receptors. However, if $GABA_A$ receptors were activated and/or NMDA receptors were antagonized, cells would undergo apoptosis. Thus, it appeared as if anesthetics could interfere with normal brain development, trick neurons that were not destined to undergo apoptosis, and impair neurocognitive development, at least of the developing newborn rodent. The importance of the activity of these receptors during this period of rapid synaptogenesis cannot be overstated.

When these same researchers conducted parallel studies on concussive brain injury in newborn rats, they surprisingly found widespread apoptosis in the brain contralateral to the site of the excitotoxic head injury [18]. Suspecting that the anesthetic was responsible for these findings, they administered NMDA-receptor antagonists to otherwise normal newborn rats and found widespread apoptosis in the brain [1, 18]. They speculated that as in the case of alcohol, other NMDA-receptor antagonists such as ketamine and nitrous oxide could induce similar injury in the form of apoptosis in the brains of human infants who received anesthesia. In addition, they postulated that $GABA_A$-mimetic anesthetics might

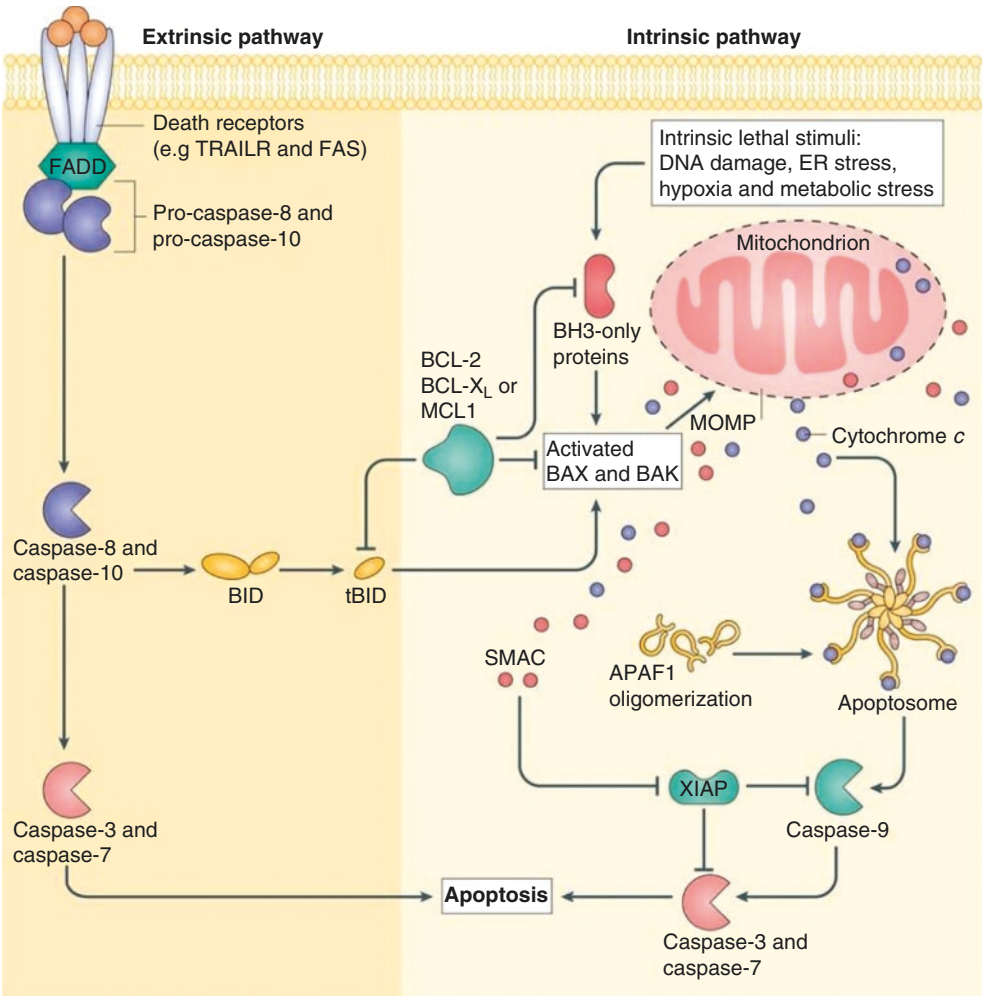

Fig. 18.1 Apoptotic neurodegeneration occurs via activating both the intrinsic and extrinsic pathways. The intrinsic pathway disrupts synaptic signaling via NMDA receptor antagonists, which upregulates Bax and increases mitochondria permeability, releasing cytochrome c into the cytoplasm, which in turn activates caspase-9 and then caspase-3, the final common pathway to apoptosis. The alternate pathway is the extrinsic pathway, which triggers cell surface death receptors that activate FAS and FADD, which in turn convert caspase-3 to its active form, initiating apoptosis. Inflammatory mediators such as TNF-alpha are one such mediator. Anesthetics may activate this pathway via $GABA_A$, thereby activating caspase-8, which then cleaves caspase-3 and initiates apoptosis. The final common pathway and the most important biomarker for the identification of apoptosis are caspase-3 levels in tissues. Downloaded from http://biologydictionary.net/apoptosis/ (accessed July 12, 2021)

also induce widespread apoptosis in humans [19]. Since most anesthetic agents exert their anesthetic effects via antagonism of NMDA receptors and activation of $GABA_A$-ergic receptors, researchers raised the biologically plausible notion that the short- and long-term neurocognitive dysfunction reported in newborn animals may cause similar effects in human neonates and infants during rapid synaptogenesis.

More than 1000 studies that investigated the relationship between anesthetics and neurotoxicity in neonatal rodents, mammals, and primates have been published. The majority of these studies demonstrated that anesthetics impair cognitive development in newborn animals. Here, we summarize the animal evidence regarding neurotoxicity during anesthesia.

At What Age Are Animals Particularly Vulnerable to or Safe from Neurocognitive Effects of Anesthetics?

Normal human brain development is a complex process that occurs over many years, which contrasts with the much-abbreviated brain growth in rodents and nonhuman primates. Normally, neurons grow, migrate, and establish vital connections throughout the growth period, although those neurons that are identified to be redundant or nonfunctional are "pruned" and removed by a naturally occurring process called apoptosis. During rapid synaptogenesis or rapid brain growth spurt, exposure to compounds that interact with NMDA or $GABA_A$ receptors is known to trigger apoptosis at rates that exceed the naturally occurring pattern or interrupt dendritic arborization, which results in nonfunctional neuronal connections by several orders of magnitude. If extensive, this leads to neurocognitive impairment in the short term as well as long term into adulthood [20]. The age at which animals are particularly vulnerable to blockade of NMDA receptors or activation of GABA-ergic receptors, i.e., during the period of rapid synaptogenesis, varies among animals. In the case of young rodents, rapid synaptogenesis occurs between postnatal days (PND) 4 and 10, with the maximum vulnerability reported to be on PND7 [21]. Evidence suggests that anesthetics induce apoptosis via blockade of NMDA blockade or GABA-mimetic activity by triggering both the intrinsic and extrinsic intracellular pathways, with the former activated earlier than the latter [21]. In rhesus monkeys, this period of greatest synaptogenesis corresponds to the period from the third trimester until PND35 [3, 22, 23]. In terms of the $GABA_A$ receptor, some evidence suggests that neurocognitive impairment is more likely to occur in early development while GABA is an excitatory neurotransmitter rather than in later development when it is inhibitory. In humans, this occurs prenatally whereas in rats, it occurs at approximately PND7 [8, 21, 24, 25].

In humans, the period of rapid synaptogenesis is thought to span development from the third trimester of pregnancy until 3 years of age [23, 26, 27]. However, the period of vulnerability to anesthetics may well extend beyond this period as evidence from animals suggests that rapid brain development or the period during which anesthetics may induce widespread apoptosis may occur in stages, that is, some regions of the brain (from the caudate nucleus to olfactory nucleus) are more vulnerable than others at specific times throughout development [21]. Although investigators have focused on specific areas of the brain in rodents such as the thalamus, hippocampus, and dentate gyrus on PND7, other areas of the brain develop more slowly and may be affected by anesthetics at later ages. The same almost certainly holds for humans with the period of rapid synaptogenesis extending over a much greater period, possibly increasing the period of vulnerability to anesthetics in some parts of the brain beyond even the 3-year limit. Thus, if apoptosis exists in humans, it may be relevant not only during fetal exposure but also during neonatal, infant, and throughout childhood.

To compare the relative developmental ages of different animals, data from core developmental stages in animals and mammals were integrated into an up-to-date statistical model known as "translating time," which can be accessed for free at the website www.translatingtime.net [29, 30]. For example, the website indicates that the developmental stage of a rodent cerebral cortex at PND7 corresponds to the maturational stage of the human brain at the very beginning of the third trimester [29, 30]. Hence, studies of anesthetic-induced apoptosis and neurocognitive dysfunction in PND7 rodents correspond to anesthetizing preterm neonates. However, rapid synaptogenesis is not a homogeneous process, affecting all areas of the brain similarly at the same time. Thus, translating the animal evidence to humans fails to account for the fact that different areas of the brain undergo rapid growth and pruning at different times throughout early childhood. In contrast to research in animals where brain biopsies and cellular and subcellular brain studies are possible, research in humans is limited to test only functional human responses for ethical reasons.

To date, no clear cutoff (translated) age can be identified at which there is no risk of structural or functional abnormalities. Thus, if this problem exists in humans, it may not only be relevant to intrauterine exposure but go beyond early infancy.

Similarly, no defined duration of exposure can be identified in in vivo animal studies. These studies examine substantially longer exposure times than ever necessary in clinical practice and suggest abnormal structural and detrimental cognitive outcomes after prolonged exposure including in nonhuman primates [21, 24, 25, 31–35]. The need to either combine or separate interventions also remains unanswered.

Does the Duration of Exposure Impact Long-Term Effects?

The minimum duration of exposure to putative anesthetics beyond which widespread apoptosis occurs has not been defined in newborn animals, but the evidence shows that brief exposure to proapoptotic anesthetics including ketamine and sevoflurane does not trigger widespread apoptosis, even in PND7 rodents [36]. In most animal studies, anesthesia was administered for periods two- to threefold greater than the duration of most anesthetics in human infants <1 year of age [32, 37–42]. We speculate that the purpose of exposing newborn animals to prolonged anesthesia was to achieve extensive apoptosis and ensure cognitive impairment to report neurocognitive dysfunction, irrespective of its relevance to the human anesthetic experience. Moreover, anesthetics induce the maximum harm to the brains of newborn animals if it is administered during the most vulnerable period of brain growth, the period of rapid synaptogenesis. The duration of synaptogenesis in newborn rodents is approximately 1% of that in human neonates, rendering these precocial rodents/animals much more vulnerable to the effects of anesthesia on synaptogenesis than in humans.

Do All Anesthetic Agents Cause Neurocognitive Dysfunction?

Except for xenon, opioids, neuromuscular blocking drugs, and possibly alpha$_2$ agonists, all other anesthetic agents cause neuroapoptosis as well as neurocognitive dysfunction in the brains of animals from newborn rodents (mice, rats, and guinea pigs) to nonhuman primates and mammals. In animals, a single anesthetic exposure may be insufficient to trigger massive apoptosis or demonstrable short- and long-term neurocognitive changes, but when multiple drugs are administered concurrently or larger doses are administered over a period, the probability that they cause neurocognitive changes increases dramatically. Hence, exposing children to a single putative anesthetic may not cause neurocognitive dysfunction at least in small doses, whereas when exposing them to a combination of anesthetics, either repeatedly or after prolonged exposure, the severity of the defect increases substantively.

Intravenous Anesthetics

With the exception of the alpha$_2$ agonists, all intravenous anesthetics can cause neuroapoptosis and neurocognitive dysfunction in newborn animals by their known interactions with NMDA and GABA$_A$ receptors. These putative anesthetics confer their effects on neuronal tissue in similar regions of the central nervous system and by similar mechanisms. In sum, the effects of the potentially neurotoxic anesthetics depend on the dose, duration, and frequency of administration to maximize their proapoptotic effects and neurocognitive impairment.

Ketamine. Ketamine, the best known NMDA-receptor antagonist, has been extensively studied in newborn animals. It causes widespread apoptosis and neurocognitive dysfunction [22, 38, 43]. However, the dose of ketamine (as well as most other intravenous anesthetics) required to induce anesthesia in animals is five- to tenfold greater than the dose in humans [38, 44]. For example, the plasma concentrations of ketamine that induce anesthesia in newborn animals, 14 μg/mL, are five- to tenfold greater than those in humans, 2–3 μg/mL [44]. Since these large doses of ketamine are required to induce anesthesia in animals, the same doses were administered to assess the severity of the apoptosis and neurocognitive dysfunction in newborn animals; whether these same effects are present in neonatal humans at much smaller doses of ketamine has not been forthcoming.

In rats, when ketamine was given on PND7 and repeated thereafter, it caused neurodegeneration and apoptosis [44] within the laterodorsal thalamic nucleus of rats. Indeed, the apoptotic effects of ketamine likely are regionalized to the limbic areas of the brain as NMDA receptors are highly expressed in this region of the brain in PND7 rats [45]. Ketamine exerts multiple effects in the hippocampal dentate gyrus including inhibiting neuronal differentiation, proliferation, and migration, which may explain how ketamine given to newborn rodents on PND7 leads to neurocognitive dysfunction in adult rodents [46]. In the long term, a single dose of 20 mg/kg s/c ketamine in PND7 rats not only causes apoptosis in the hippocampus within 24 h but leads to impaired short-term memory and enhanced motor performance in adults [47]. In mice, ketamine-induced apoptosis depended on both age and activity, the latter attenuating the severity of the apoptosis and resultant neurocognitive dysfunction as has been reported in other models [48]. In rhesus monkeys between PND5 and PND35, ketamine-induced neuronal cell death depended on age and the duration of exposure [38, 39]. Specifically, when ketamine was infused for ≥6 h, neurocognitive changes were demonstrable; however, when it was administered for ≤3 h, there was no evidence of apoptosis [40]. In fetal macaque exposed to ketamine infusion for 5 h, apoptosis was 2.2-fold greater than it was in the neonatal brain [24]. A single 24-h exposure to a ketamine infusion in PND5 or PND6 monkeys demonstrated neurocognitive dysfunction for up to 3.5 years of age [49]. Interestingly, ketamine demonstrates antiapoptotic and anti-inflammatory roles via some growth factors (known as neurotrophins) attenuating neurocognitive impairment after isoflurane exposure [36]. Consequently, it is difficult to translate the neuroapoptotic effects of large doses of ketamine for prolonged periods in rodents to humans, who require but a fraction of

the dose for a relatively brief period to achieve comparable levels of anesthesia for surgeries.

Benzodiazepines: Enhancing the gamma-aminobutyric acid at $GABA_A$ receptors also increases neuronal apoptosis and impairs neuronal differentiation [22]. Examples of animal studies that demonstrate this include a study which showed that midazolam blocks calcium oscillations, which themselves mediate neuronal differentiation and synaptogenesis. The net effect is reduced synaptic integrity [50]. When diazepam was administered to rats on PND7, it induced widespread apoptotic neurodegeneration [51]. In an early study, midazolam in a dose of 3–9 mg/kg or nitrous oxide 50–150% failed to induce widespread neuroapoptotic degeneration, whereas when midazolam was followed by 0.75% isoflurane or combined with ketamine (≥20 mg/kg), widespread apoptosis ensued [2, 43].

Propofol: Propofol exerts both NMDA-receptor antagonism and $GABA_A$-ergic potentiation (as well as activation of $GABA_A$ receptors at larger concentrations). In newborn animals, propofol causes widespread apoptosis, impaired neuronal differentiation, and behavioral changes compared with no anesthesia [22, 32]. In PND7 mice, 6 h of IP propofol was more likely to cause apoptosis in the cerebral cortex and hippocampus than in other regions of the brain [52]. Apoptosis occurred only in neurons, but not in astrocytes, oligodendrocytes, or neural stem cells. In PND5 and PND7 rats, repeated doses of propofol for three consecutive days triggered significant decreases in dendritic spine density in the hippocampus that persisted into adulthood with cognitive deficits [53, 54]. A single dose of 50 mg/kg intraperitoneally in PND7 rat pups yielded apoptosis and cognitive deficits on PND9, whereas multiple doses induced significant neuronal apoptosis and synaptic loss at PND9 to PND35 and spatial learning and memory impairment at PND36 to PND41 [55]. In PND5 rats anesthetized with propofol for 6 h, structural changes in neural circuitry (dendritic arborization and synaptogenesis) occurred during rapid synaptogenesis [31]. Repeat dosing of propofol to PND7 rats induced greater apoptosis (in the cortex and hippocampus) and neuronal loss as well as learning and memory deficits compared with a single exposure [56]. To define the timing of maximum apoptosis during propofol administration in mice brain, continuous caspase-3 activation was measured in hippocampus CA1 neurons in vitro [57]. Caspase-3 activation was significant 5 h after the start of exposure and not before. It is tempting to conclude that activation of apoptosis is a time-dependent process that requires a startup period that may exceed the duration of anesthetic exposure in most surgeries in neonates and young children. If this holds in humans, it may explain the rarity of adverse neurocognitive outcomes in humans. The cytokine (inflammatory, caspase-3) and apoptotic responses in the hippocampus in PND7 rats who underwent appendectomy or sham surgery to propofol between 0 and 100 mg/kg intraperitoneal for 5 days demonstrated no response at 50 mg/kg in a single daily dose, whereas the larger doses (100 and 150 mg/kg) did upregulate cytokines and impair cognition [58]. Repeated but not single doses of IP propofol in mice PND7–PND11 impaired neurocognitive and behavioral abilities in adulthood [59]. The contribution of hypoxia to propofol-induced apoptosis should not be underestimated. In PND7 mice, 18% oxygen exacerbated the severity of apoptosis and cognitive learning deficits compared with those who remained normoxic [60]. Quantifying the location of apoptosis in monkeys revealed an age-related effect: exposing the fetus to propofol resulted in apoptosis in the subcortical and caudal regions of the brain, whereas exposing the newborn monkey resulted in apoptosis in the neocortical regions [32]. Overall the severity of the apoptosis after 5 h of propofol was less than comparable doses of isoflurane [61]. A recent study suggested that the addition of propofol to a ketamine anesthetic attenuates ketamine-induced cognitive dysfunction [62]. Several factors may affect the extent of apoptosis during propofol anesthesia. Propofol, particularly in repeated doses in newborn rodents and monkeys, triggered apoptosis and impaired cognition that persisted into adulthood.

α2 agonists: α2 agonists are not proapoptotic anesthetics because they neither antagonize NMDA receptors nor potentiate $GABA_A$ receptors but exert their actions on the locus coeruleus (specifically the ventrolateral preoptic nucleus) via α2 receptors and the sympathetic nervous system [63]. α2 agonists are neuroprotective (via intracellular brain-derived neurotrophic factor), and in the presence of proapoptotic anesthetics such as isoflurane or midazolam in PND7 rats, they attenuate the severity of the apoptosis by increasing Bcl-2 (B-cell lymphoma/leukemia-2 regulatory proteins) and expression of the mitogen-activated protein kinases (MAPK), JNK (c-Jun N-terminal kinase), P38 MAPK, and ERK (phosphorylated, extracellular signal-regulated protein kinase) [63–65]. In a systematic review of the neuroapoptotic effect of dexmedetomidine in animals, dexmedetomidine did not cause apoptosis but attenuated the injury of coadministered proapoptotic agents [66]. α2 agonists attenuate sevoflurane, isoflurane, and propofol-induced apoptosis in newborn rats by upregulating Bcl-2 expression and reversing the proapoptotic suppression of Bcl-2 [67–70]. Dexmedetomidine exerts a biphasic effect on neurotoxicity: in PND7 rats, small or clinically relevant doses of dexmedetomidine 50–100 μg/kg intraperitoneally (IP) alone was not proapoptotic, whereas large doses ≥250 μg/kg IP over 6 h was proapoptotic, similar to ketamine alone [71]. In addition, dexmedetomidine did not attenuate ketamine-associated apoptosis. These results are consistent with the neuroprotective effects of small doses of dexmedetomidine (1 μg/kg IP) during sevoflurane anesthesia reducing the severity of the apoptosis by 84% in the thalamus and 50% in the hippocam-

pus and cortex, but increasing mortality with larger doses >5 μg/kg IP [72]. In contrast, repeat doses of dexmedetomidine up to 20 μg/kg IP during sevoflurane or even 100 μg/kg IP 2-hourly failed to substantively attenuate apoptosis in PND7 rats anesthetized with sevoflurane in other studies [73, 74]. Dexmedetomidine also attenuates propofol-induced apoptosis and neurocognitive impairment in newborn rats [36]. The inconsistency of the effects of dexmedetomidine among these studies raises questions regarding the use of the neonatal rat as a model to extrapolate its effects on vulnerable infants and children [75].

Clonidine, an older α2 agonist with less affinity for the α2 receptor than other α2 agonists, shares many of the effects of dexmedetomidine. Similar to dexmedetomidine, clonidine also confers neuroprotective effects in at least one preclinical study [76].

Opioids: Opioids act via mu, kappa, and delta receptors to exert their primary action, not on NMDA or $GABA_A$ receptors. However, some cells in the central nervous system such as oligodendrocytes express opioid receptors and thus may respond to opioids if they are administered during periods of rapid growth.

Methadone and buprenorphine cross the placenta exposing the fetus to opioids. Prenatal exposure to methadone has been associated with microstructural changes in major white matter tracts in the fetus at birth, although a cause and effect relationship remains to be established [77, 78]. The mechanism postulated for methadone- and buprenorphine-induced neurodysfunction is through their interactions with dopamine, serotonin, and cholinergic receptors as well as through oligodendrocyte-expressed opioid receptors. The latter may impair and alter myelination and white matter microstructures in the developing brain [77–79]. In a clinical study of women who abused opioids throughout their pregnancy, naltrexone offered an alternative to these two opioids although it should be withheld 60 h before delivery [80].

The evidence that the opioids, morphine, fentanyl, and remifentanil may be associated with apoptosis in newborn rodents depends on the duration of exposure. Newborn rodents that received morphine for <24 h and did not undergo surgery sustained no irreversible structural changes in their brains, whereas rats that received opioids for 5 days sustained irreversible structural changes (in microglia or oligodendrocyte) and apoptosis [81, 82]. In a similar study, PND7 rats that received morphine for the first 6 days after birth developed increased apoptosis only in the cortex and amygdala, but not in the hippocampus, hypothalamus, or periaqueductal gray matter and almost exclusively in neurons, not glial cells [83]. Long-term exposure to morphine resulted in significant apoptosis in microglia and neurons, an effect reversed by naloxone [84]. This evidence supports the hypothesis that prolonged opioid exposure can induce widespread apoptosis in newborn rodents.

Studies of IV fentanyl with or without xenon in newborn pigs failed to produce evidence of apoptosis (using caspase-3 immunostaining) after a 24-h infusion of fentanyl [85]. However, a subsequent study documented apoptosis in the cerebellum of newborn pigs after a similar infusion [86].

Remifentanil is known to induce postoperative hyperalgesia, an effect mediated through μ-opioid receptor activation of NMDA receptors [87]. Hence, it follows that during rapid synaptogenesis, remifentanil (which contains glycine) may promote necrotic and/or apoptotic cell death in vulnerable animals. In PND2 mouse brain slices ex vivo, a 5-h infusion of remifentanil increased necrotic cell death in the deep layers of the neocortex and decreased apoptosis in the superficial immature layers [87]. Remifentanil decreased both the intrinsic and extrinsic apoptotic pathways as evidenced by the caspase-3, caspase-8, and caspase-9. The effects of remifentanil on apoptosis have also been studied in the presence of isoflurane anesthesia in newborn (PND7) rats. Remifentanil did not augment apoptosis during isoflurane anesthesia but demonstrated neuroprotection in the hippocampus [88]. Hence, acute, brief exposure to opioids during anesthesia and the perioperative period likely holds minimal risk for the neonate. Further research is warranted to identify the possible neurocognitive effects of prolonged exposure to opioids in neonates.

Intravenous vs. Inhaled Anesthetic Neurocognitive Effects

When comparing the physiologic effects of intravenous and inhalational anesthetics, the greatest challenge to overcome is to ensure that equivalent levels of anesthesia are present for both. Although the depth of anesthesia with the inhalational anesthetics can be estimated by measuring the end-tidal concentration, a comparable metric for intravenous anesthetics has not been forthcoming. The depth of anesthesia with intravenous agents can only be estimated using electroencephalography.

The only study that compared the severity of apoptosis with an intravenous and inhalational anesthetic [4] included two trials in nonhuman primates that compared 5 h of propofol [32] with 5 h of isoflurane [33]. The results yielded slightly less apoptosis with propofol than isoflurane.

Inhalation Agents

All inhalation agents except for xenon [85, 89] trigger neuroapoptosis and neurocognitive dysfunction in neonatal animals. Isoflurane, sevoflurane, and desflurane all increase neuroapoptosis in animals from newborn rodents to monkeys, in proportion to the dose, duration of exposure, and

frequency if repeated [33, 34, 41, 85, 89–103]. However, differing doses and single anesthetic administrations have made it difficult to compare the relative risk of neurocognitive dysfunction after the current anesthetics, isoflurane, sevoflurane, and desflurane. The minimum alveolar concentration (MAC) or the end-tidal concentration of inhalational anesthetic, the effective dose that prevents movement in 50% of the animals or patients (ED_{50}), is the clinical metric widely used to compare equipotent concentrations of inhalation anesthetics. The MAC values for inhalation anesthetics are stable across species [104]. Hence, many studies report "MAC" multiples or fractions of anesthetics to provide equipotent concentrations among studies.

Single Inhalational Agents

Multiple studies examined the neuroapoptotic and neurocognitive effects of individual anesthetics in rodents and nonhuman primates during the period of rapid synaptogenesis. Isoflurane, the first inhaled agent studied, in PND7 mice (not in PND4 or 14 mice) at sub-MAC concentrations 0.75% for 4 h, 1.5% for 2 h, or 2.0% for 1 h, and in separate studies, 0.75% and 1.5% isoflurane for 6 h triggered widespread apoptosis compared with controls while maintaining euglycemia [90, 92, 103]. However, a prior study reported that 1.5% isoflurane for <6 h did not cause widespread apoptosis in hippocampal slices from PND7 mice, but did at durations ≥6 h [41]. Investigators posited that hypercapnia may explain the inconsistency in these results, as hypercapnia itself leads to apoptosis in a similar distribution in the brain as 4 h of 1 MAC isoflurane, although only the latter, not hypercapnia, exposure resulted in long-term neurocognitive dysfunction [105].

Recent evidence also suggested that brief exposure to isoflurane once at differing ages, PND3, PND5, and PND7 as well on pairs of days or all 3 days, yielded neuroapoptosis of varying severity in different regions of the brain: PND3 affected the thalamus, PND5 affected the hippocampus and striatum, and PND7 affected the cortex [106]. This likely reflects the distribution of NMDA and $GABA_A$ receptors in the different parts of the brain on different postnatal days. Repeated exposure to isoflurane-induced apoptosis as well as behavioral dysfunction. In PND7 rats anesthetized with 1.8% isoflurane for 2 h either once or repeated on PND10 and PND13, those after a single exposure demonstrated improved spatial memory, whereas those after multiple exposures experienced impaired cognitive dysfunction [107].

In fetal rhesus macaques at 120-day gestation, 5 h of 1–1.5% end-tidal isoflurane administered to the pregnant rhesus macaques caused substantive apoptosis of neurons (primarily in the cerebellum, caudate, putamen, amygdala, and other regions) and oligodendrocytes (diffusely over several white matter areas) [33]. In PND6 rhesus macaques, 5 h of isoflurane between 0.7 and 1.5% isoflurane yielded substantive apoptosis primarily limited to the cerebral cortex [93]. In a similar study, the same group determined that the apoptosis after 5-h isoflurane was evenly divided between glial cells and neurons [94]. To determine whether isoflurane induces neuroapoptosis in young nonhuman primates and, if it does, the spatial distribution of the apoptosis in the gray and white matter, PND6 rhesus macaques were anesthetized with isoflurane at a surgical depth of anesthesia for 3 h [95]. Apoptosis occurred fourfold more frequently in those anesthetized with isoflurane compared with controls. Moreover, the distribution of the apoptosis differed: neuroapoptosis occurred primarily in the cortex, caudate, putamen, and thalamus, whereas oligodendrocyte apoptosis was evenly distributed throughout the white matter [95]. In terms of the behavioral follow-up after an anesthetic exposure, long-term behavioral changes in both motor and socioemotional functions were demonstrated in PND6 rhesus macaques that were anesthetized with isoflurane for 5 h on three occasions, findings that were not present in either controls or those exposed to a single anesthetic [108].

Sevoflurane, the most widely used inhaled agent in children, has also been shown to induce apoptosis in PND7 rats together with spatial learning deficits 6 weeks after exposure [109]. In PND7 rats, 2.3% sevoflurane for 6 h induced widespread neuroapoptosis in the hippocampus but not for ≤1.3% for the same period [110]. These results were supported in a second study in which 3% for 6 h in PND7 rats induced widespread apoptosis in the frontal cortex and CA1 region of the hippocampus but not 2% sevoflurane for 3 h [111] and a second study that showed 3% sevoflurane for 6 h impairs synaptic plasticity in the hippocampus and learning and memory deficit compared with a 1-h exposure [112]. Curiously, in a study that investigated the effects of low concentrations of sevoflurane on cognitive development, 1.8% sevoflurane promoted hippocampal neurogenesis and facilitated performance in learning tasks [113].

To compare the neuroapoptotic and long-term cognitive effects of a single prolonged exposure to multiple brief exposures of sevoflurane, several studies were undertaken. In the first, PND7 rats were anesthetized for either 2 or 6 h in a single exposure or repeated 2 h exposures on PND7, PND10, and PND13 (total 6 h) or no sevoflurane [96]. Repeat exposure to sevoflurane causes greater postsynaptic losses than a single exposure. In the second, the long-term cognitive effects of sevoflurane in newborn mice, PND3 to PND14, that were exposed to sevoflurane between 1 and 4% for intervals between 1 and 4 h were investigated [114]. After a single exposure, younger mice yielded worse cognitive dysfunction in adulthood than did older mice; greater concentrations of sevoflurane and more frequent exposures also yielded worse cognitive dysfunction in adults. Lastly, the smaller the interval between repeat exposures, the worse the cognitive dysfunction. In contrast, PND7 rats that were exposed to 2.5%

sevoflurane for 2 h once or also on PND10 and PND13 for the same duration failed to demonstrate cognitive impairment in adulthood [115]. These results suggest that very young rodents are particularly susceptible to the long-term effects of sevoflurane if exposed to a threshold concentration.

Pairwise Comparisons

Do the inhalational anesthetics differ in their propensity to induce widespread apoptosis or cognitive dysfunction in the short and long term? In pairwise comparisons, isoflurane was compared with sevoflurane at 0.5 MAC in PND7 mice for 6 h. Apoptosis in the hippocampus and cortex was significantly greater with isoflurane than sevoflurane, but neither altered memory nor learning abilities [91]. Using the same model, isoflurane at 1 MAC for 6 h caused both short-term and long-term memory impairment, whereas sevoflurane caused only long-term impairment [102]. Recent evidence indicates that while both isoflurane and sevoflurane induce apoptosis, they act via different mechanisms. Isoflurane but not sevoflurane induces neuroinflammation and alters the expression of proteins that impact synaptic transmission and memory in mice suggesting a differential effect between these two agents [103].

To study the effects of repeated dosing, isoflurane 1.5% for 2 h/day for 3 days caused greater cognitive impairment at 30 days compared with sevoflurane 2.2% with the same regimen, although both cause similar apoptosis of hippocampus neurons and neuronal damage [116].

When PND7 rats were administered with either sevoflurane or the combination of sevoflurane and nitrous oxide at 1 MAC for 4 h, only rats who were exposed to the combination of anesthetics displayed impaired memory and behavior in adults [117]. These results supported the notion that combinations of anesthetics are more toxic than exposure to individual agents. The same investigators administered 1 MAC isoflurane or desflurane to PND7 rats for 4 h [118]. Apoptosis was present in the thalamus, hippocampus, and dentate gyrus. At PND48, both anesthetics caused memory impairment and cognitive dysfunction, but isoflurane appeared to produce worse memory and cognitive dysfunction.

Comparison of Three Inhalational Anesthetics

Two studies compared the neurocognitive effects of equipotent concentrations of inhalational anesthetics in PND6/PND7 mice. In the first study, desflurane yielded greater apoptosis and spatial long-term memory impairment than both sevoflurane and isoflurane [100]. In a second study, the three inhalational anesthetics yielded similar neurotoxic effects [101]. Slight differences in the methods of the experiments may have accounted for these differences.

Further evidence suggested that inhalational agents may interfere with neural development even when administered to older animals. PND16 rats administered with 1 MAC isoflurane, sevoflurane, and desflurane for up to 2 h increased dendritic spine density without inducing widespread apoptosis or changes in dendritic arbor patterns, thereby interfering with brain circuit assembly in the cerebral cortex [35]. These authors suggested that PND7 in the rodent model may correspond more closely to the first to the second trimester of pregnancy in humans and that PND16 more closely approximates the first few years of postnatal life on the human scale, a thought that merits consideration when extrapolating nonhuman primate data to humans [29, 30].

All three inhalation anesthetics are considered equally neurotoxic in young rodents, although whether desflurane has a greater propensity to trigger apoptosis than the other two anesthetics at equipotent concentrations remains unclear.

Nitrous oxide: In an early study, PND7 rats that were exposed to only nitrous oxide for up to 6 h experienced no neurocognitive dysfunction [2]. The same holds for isoflurane alone. However, when the combination of midazolam, nitrous oxide, and isoflurane was administered, the last two for 6 h in PND7 rats, the severity of the neuroapoptosis was 28-fold greater than either nitrous oxide or isoflurane alone [2].

Xenon: Xenon is a rare noble gas with a very small blood/gas partition coefficient (0.007) that equilibrates rapidly within the brain when administered by inhalation. It is a weak anesthetic with a MAC of 70%. Xenon (75%) attenuates isoflurane-induced apoptosis [89, 119], although it may trigger apoptosis [119]. In contrast, when xenon (50%) was given to newborn pigs for 24 h, it did not induce apoptosis compared with fentanyl [85]. Xenon's mechanism of action is thought to involve partial antagonisms of the NMDA receptor (differently from other anesthetics). Nonetheless, it is either weakly or non-apoptotic during rapid synaptogenesis. The major drawbacks with xenon are its expense, limited availability (it is a naturally occurring gas), and the fact that it must be administrated in a closed circuit to be economical [63].

Is There a Difference Between Single and Multiple Exposures or the Duration of Exposure on Apoptosis?

Most, but not all, laboratory investigations have reported apoptosis and neurocognitive dysfunction after a single exposure to anesthetics. Although experimental deficiencies including insufficient doses or duration of exposure may explain the false-negative results, in most cases, a single exposure causes neurological deficits in animals (albeit transiently). For ketamine, propofol, isoflurane, and sevoflurane, multiple exposures resulted in greater apoptosis and neurocognitive dysfunction than single exposures. In the case of ketamine, a single dose of 10 mg/kg intraperitoneally or even 3 h of infusion in rats and subhuman primates failed to trig-

ger apoptosis (using caspase-3 as the marker of apoptosis) compared with controls, whereas continuous infusions of 20–50 mg/kg/h for 24 h or repeat doses of 20–40 mg/kg triggered widespread apoptosis [38, 43]. Interestingly, even seven repeat doses of 10 mg/kg failed to trigger apoptosis in the laterodorsal thalamus and medial amygdala, whereas seven repeat doses of 20 mg/kg did trigger apoptosis in these two regions [44]. Although animals require doses of intravenous drugs that are severalfold greater than in humans to induce anesthesia, the blood concentration of ketamine in animals (14 mcg/mL) is three- to sevenfold greater than that in humans (2–5 mcg/mL). In newborn rodents and subhuman primates, very large anesthetic doses, multiple doses, or doses administered for prolonged periods induced apoptosis (Table 18.2), although how this evidence translates to humans remains unclear.

Are There Any Preventative Measures or Treatments That May Attenuate This Insult?

During studies of head injury in rodents, investigators reported that injured rats performed poorly when compared with the sham controls; however, if they exercised the rats after the head injury, the injured rats performed as well as the sham controls [120]. This prompted a multifaceted investigation into the beneficial effects of exercise and socialization after exposing newborn animals to anesthesia. The authors determined that if the newborn rats were exercised and socialized after anesthesia, the neurocognitive effects were drastically attenuated. If rats in many of these earlier studies were isolated, not exercised, and not socialized, widespread neurocognitive effects may have been exaggerated [121]. Most neonates and infants are held by parents, cuddled, and stimulated after sedation or anesthesia, which may contribute to the difficulty in identifying adverse effects in humans after anesthesia.

A bevy of pretreatments has been effective in attenuating both apoptosis and neurocognitive dysfunction in newborns and the elderly [36]. These include ketamine preconditioning, lithium, budesonide, NAP (neuroprotective peptide, davunetide), vitamin C, bumetanide, melatonin, and TRP-601 [36, 120, 122–131].

Translation and the Effects of Surgery

Despite the large volume of animal studies available that demonstrate structural and behavioral changes after exposure to various anesthetic agents in vitro, we lack comparable evidence from human studies. The translational relevance of animal studies is challenging to define due to several factors. Whether the immature brain in the animal is comparable to the developing human brain at various stages of childhood has been debated. Numerous compounds that were identified in the laboratory as poisons proved to be safe in humans [132]. Only two of the hundreds of animal studies that investigated neuroapoptosis in animals included animals undergoing surgery; in humans, anesthesia is most commonly administered to facilitate surgery and infrequently for noninvasive procedures (such as CT or MRI scanning). The results of those two studies yielded conflicting effects in the presence of surgery. Although 100% of newborn animals are adversely and demonstrably affected by exposure to anesthesia in these studies, serious neurocognitive adverse outcomes in humans are so exceedingly rare that it has neither been recognized after anesthesia in young children after almost a century of providing general anesthesia nor recognized in long-term studies [132]. To further compound this issue, the time lag between anesthetic exposure and the development of frank cognitive dysfunction may further complicate the issue. Many have questioned the relevance of the neurocognitive effects after intravenous anesthetics in newborn animals as the doses and duration of exposure have been several orders of magni-

Table 18.2 Effects of anesthetic agents on rodents and nonhuman primates

	Agents	Cellular effects	Neurobehavioral findings
Rodents	Ketamine Isoflurane/ sevoflurane Propofol Combined agents Modifiers (+) Modifiers (−)	Neuroapoptosis Neurodegeneration Neuroinflammation Defects in: • Neurogenesis • Growth cone polarization • Cytoarchitecture • Dendritic density Noxious stim (+) isoflurane Noxious stim (−) ketamine	• Learning • Spatial memory • Motor activity • Attention • Social behavior • Behavior Not available (−) Sevoflurane • Anti-inflammatory agent • Environment enrichment
Nonhuman primates	Ketamine	Neuroapoptosis Neurodegeneration	Learning, memory, motivation, response speed, color discrimination
	Isoflurane propofol	Neuroapoptosis Apoptosis in neurons and oligodendrocytes	Not available Not available

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tude greater in the animal studies (10- to 20-fold greater doses of ketamine in animals than in humans) and approximately 5.5 h ±4 h than in routine surgery in young children [4, 133]. Stimulating neonates and infants as most nurses and parents do after surgery may attenuate the neurocognitive effects in humans. The newborn animal is a delicate preparation with up to 30% of the animals succumbing during the first several hours of the study; [121] such a mortality rate suggests the model is quite unstable and in no way reflects the human under general anesthesia, whether it is 26 weeks gestation or 50 weeks postnatal age. Difficulties in translation from animals to humans due to the differences in physiology including accelerated "pace of life" and sexual maturation in rats preclude experimental equivalence in humans [134].

Numerous laboratory issues may bias the evidence from animal studies rendering them not applicable to humans. Initial concerns regarding the effects of anesthesia on PND7 rodents were attributed to hypoglycemia, acidosis, and hypoxia, which were subsequently corrected in follow-up studies. However, other issues persisted including high mortality rates [40–50%] reported in the newborn rodent studies, without clear explanations for the large percent of deaths [114, 121]. Whether this speaks to the fragility of the rodent model is unclear, but similar mortality rates do not occur in neonatal humans under anesthesia. Additional issues may explain the discrepant results including the breeds of rodents, feeding, local infection risks, and handling or other as yet unidentified factors. In none of the studies has surgery been performed, the primary indication for general anesthesia. Some have reported that surgery itself may increase apoptosis, further complicating the interpretation of research into the effects of anesthesia on apoptosis in humans [135]. Nociceptive stimulation in the presence of a proapoptotic anesthetic such as isoflurane augmented neuroapoptosis but in the case of ketamine attenuated neuroapoptosis [136, 137]. Curiously, social isolation and enrichment deprivation have been shown to exacerbate neurocognitive deficits in newborn rodents after anesthesia [138]. Correcting these deficiencies attenuated the impaired neurobehavioral outcomes from the anesthetics [121]. A mechanism for this effect has been elucidated and may offer a target for preventing neurotoxicity [139].

Human Studies

In comparison with the numerous studies in animals, there is a dearth of clinical studies in humans. Given the ethical challenges of undertaking clinical trials on neurocognitive dysfunction in children, the majority of the initial studies in humans were retrospective and/or observational. These were followed by large population studies providing a more robust assessment of neurocognitive outcomes recently, ambidirectional studies, and most recently, a single multicentered, randomized controlled trial of spinal versus general anesthesia as summarized in two reports [140, 141]. Given the inherent weaknesses in these studies, most can provide only associations among the variables, anesthesia, and the cognitive metrics. Confounding factors that limited the external validity of these initial studies included pain, (neuro-) inflammation, surgical trauma and sequelae, the underlying indications for surgery, and comorbidities, which weighed heavily in our assessment of their impact on neurological structure and function [3].

Serious criticism of the studies in humans has focused on the imprecision in the outcome variables that were used to assess and quantify possible defects in cognition. A review itemized the psychometric and nonpsychometric tests that have been used to diagnose neurocognitive impairment after anesthesia in young children (Table 18.3).

Retrospective Cohort Studies

A large number of retrospective cohort studies investigated whether exposure to general anesthesia in infants and young children is associated with neurocognitive deficits assessed using a range of metrics at a later age, some of which are cited here [142–163]. With two exceptions [142, 143], overall these studies reported (1) no association between a single exposure to anesthesia and later neurocognitive deficits and (2) an association between multiple exposures (≥2 or more) and a range of neurocognitive deficits. Although these were retrospective studies with well-recognized weaknesses, they also suffered from multiple sources of heterogeneity and bias including the age of exposure to general anesthesia, age at which the neurocognitive outcome was assessed, widely discrepant outcome variables (including learning disability, IQ testing, academic performance, early development index, ADHD diagnoses, and the Ages and Stages Questionnaire), and the absence of baseline measurements [164]. Using the Raine cohort from Western Australia, which included extensive and repeated neurodevelopmental testing, the authors asserted that group testing such as academic achievement may lack sufficient sensitivity to detect smaller, minor, or more subtle neurocognitive impairment between children exposed and not exposed to anesthesia in early life [153, 154]. Nonetheless, studies from multiple countries reached similar conclusions that multiple anesthetic exposures are more likely than not to be associated with some degree of neurocognitive deficits at a later age and that a single anesthetic exposure is unlikely to be associated.

Confounding variables that are associated with cognitive deficits have precluded investigators in some studies from

Table 18.3 List of different neurocognitive and sensorimotor function outcomes used to assess outcome in children exposed to general anesthesia (alphabetic order) and the domain to which the test was assigned

Psychometric test		Domain of testing
ABAS-II	Adaptive Behavior Assessment System—Second Edition	Development
AIMS	Alberta Infant Motor Scale	Development
–	Albert Einstein College of Medicine Neonatal Neurobehavioral Assessment Scale	Development
AVLT	Rey Auditory Verbal Learning Test	Intelligence/cognition
ASQ	Ages and Stages Questionnaire	Development
BDS	Backward digit span test	Intelligence/cognition
BRIEF	Behavior Rating Inventory of Executive Functions	Development
BSID-II	Bayley Scales of Infant and Toddler Development—Second Edition	Development intelligence
BSID-III	Bayley Scales of Infant and Toddler Development—Third Edition	Development intelligence
CAT	California Achievement Test	Academic achievement
CBCL	Child Behavior Checklist	Development
CDI	Child Depression Inventory	Screening/diagnosis (psychiatric disorder)
CELF	Clinical Evaluation of Language Fundamentals	Development
CELF-E	Clinical Evaluation of Language Fundamentals—Expressive Language Score	Development
CELF-R	Clinical Evaluation of Language Fundamentals—Receptive Language Score	Development
CELF-T	Clinical Evaluation of Language Fundamentals—Total Language Ability	Development
CHQ50	The Child Health Questionnaire 50	Development
CPM	Raven's Colored Progressive Matrices	Intelligence/cognition
CPT-II	Continuous Performance Test II	Development
CTRS-R	Conners' Teacher Rating Scale—Revised	Development
CVLT-C	California Verbal Learning Test—Children	Academic achievement
DKEFS	Delis-Kaplan Executive Function Systems/Trail Making Subtests	Academic achievement
DSM-IV	*Diagnostic and Statistical Manual of Mental Disorders—Fourth Edition*	Screening/diagnosis (psychiatric disorder)
DSM-ADH	DSM—Attention Deficit Hyperactivity Scores	Screening/diagnosis (psychiatric disorder)
EDI	Early Development Instrument	Development
FDS	Forward digit span test	Intelligence/cognition
FSIQ	Full-Scale Intelligence Quotient	Intelligence/cognition
G-TVPS	Gardner Test of Visual-Perceptual Skills—Revised	Development
GDQ	General Developmental Quotient	Development
GDS	Gesell Developmental Schedule	Development
GMDS	Griffiths Mental Development Scale	Development
GMFCS	General Motor Function Classification Score	Development
HAWIVA-III	Hannover-Wechsler Intelligence Scale, third Edition	Intelligence/cognition
GPT	Grooved Pegboard Test	Intelligence/cognition
ICD-9	International classification of Disease—Ninth Edition	Screening/diagnosis (psychiatric disorder)
ICD-9-CM 299.00	International Classification of Disease—Ninth Autistic Disorder Diagnoses	Screening/diagnosis (psychiatric disorder)
ICD-9-CM 314.01	International Classification of Diseases—Ninth Edition Attention Deficit Hyperactivity Disorder	Screening/diagnosis (psychiatric disorder)
IEP-EBD	Individualized Educational Program—Disorders of Emotion and Behavior	Academic achievement[a]
IEP-SL	Individualized Educational Program—Speech and Language	Academic achievement[a]
K-ABC	Kaufmann Assessment Battery for Children	Intelligence/cognition
KET-KID	Kognitiver Enwicklungstest für das Kindergartenalter	Intelligence/cognition
LD	Learning Disability	Screening/diagnosis
MAND	McCarron Assessment of Neuromuscular Development	Development

Table 18.3 (continued)

Psychometric test		Domain of testing
MacArthur-Bates CDI	MacArthur-Bates Communicative Development Inventory	Development
MRI	Magnetic resonance imaging	Screening/diagnosis (somatic disorder)
NEPSY	Developmental NEuroPSYchological Assessment	Academic achievement
NEPSY-2-NL	NDevelopmental Neuropsychological Assessment Development Battery—Second Edition, Dutch Version	Development
OLSAT	Otis-Lennon School Ability Test	Cognition
OWLS	Oral and Written Language Scales	Academic achievement
PDMS	Peabody Developmental Motor Scales	Development
–	Phonemic verbal fluency test	Intelligence/cognition
PIQ	Performance Intelligence Quotient	Intelligence/cognition
PPVT	Peabody Picture Vocabulary Test	Academic achievement
RDLS	Reynell Developmental Language Scales	Development
PSLE	Primary School Leaving Examination	Academic achievement
SDMT	Symbol Digit Modality Test Semantic Verbal Fluency Test	Development Intelligence/cognition
SON-R	Hogrefe/Snijders-Oomen Nonverbal Intelligence Test—Revised	Intelligence/cognition
–	Stanford	Academic achievement
SB-5	Stanford-Binet Intelligence Scales—Fifth Edition Stroop Color and Word Test	Intelligence/cognition Intelligence/cognition
TCS	Total cognitive skills	Intelligence/cognition
TIQ	Total Intelligence Quotient	Intelligence/cognition
TEA-Ch NL	Test of Everyday Attention for Children, Dutch Version	Intelligence/cognition version
TMT—A	Trail Making Test—Part A	Intelligence/cognition
VABS	The Vineland Adaptive Behavior Scale, Second Edition	Development
VIQ	Verbal Intelligence Quotient	Intelligence/cognition
VMI	Beery-Buktenica Developmental Test of Visual Motor Integration, Fifth Edition	Intelligence/cognition
Wallin BP	Wallin B pegboard	Development
WAMSE	Western Australian Monitoring Standards in Education	Academic achievement
WASI	Wechsler Abbreviated Scale of Intelligence	Intelligence/cognition
WJ III	Woodcock-Johnson III	Academic achievement
WJ III—Visual Matching	Woodcock-Johnson Test—Visual Matching	Academic achievement
WeeFIM	Functional Independence Measure	Development[b]
WPPSI-R	Wechsler Preschool and Primary Scales for Intelligence: Revised	Intelligence/cognition
WISC-III	Wechsler Intelligence Scale for Children—Third Version	Intelligence/cognition
WISC-III-NL	Wechsler Intelligence Scale for Children—Third Version, Dutch Version	Intelligence/cognition
WISC-IV	Wechsler Intelligence Scale for Children—Fourth Edition	Intelligence/cognition
Nonpsychometric tests/means to assess cognitive, developmental outcome, or both of children exposed to general anesthesia		
Serum biomarkers of brain-derived neurotrophic factor (BDNF), S100B		Neuron damage
Neurological examination		Neurologic deficit
Surrogate measures of visual function (visual acuity, refractive error, thickness of retinal nerve fiber layer)		Sensorineural deficit

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[a]Individualized educational program (IEP) is not a psychometric test but the intervention applied for a child with special needs. The IEP is meant to address each child's unique learning issues and includes specific educational goals. It is a legally binding document, sanctioned by the US federal law called the Individuals with Disabilities (IDEA). The IEP describes the goals the team (e.g., teachers, parents, school psychologists) sets for a child during the school year, as well as any special support needed to help achieve them

[b]Functional Independence Measure is used in follow-up of rehabilitation

detecting an effect of anesthesia on neurocognitive deficits. The type of surgery, which has not been a restriction in most studies, may impact the power of the study to identify the specific effect of anesthesia on cognitive function. In two such studies, one in infants undergoing neurosurgery [149] and the second in infants undergoing craniofacial surgery [150], ninth-grade exam scores were compared with controls. In the former study, the exam scores in those with hydrocephalus and craniotomy were less than controls, although those with myelomeningocele repair were similar to controls. The anesthetic did not impact the scores. In the latter study, the ninth-grade exam scores depended on the type of cleft rather than the number and timing of the anesthetics. In designing studies to investigate the neurocognitive effects of general anesthesia in infants, it is prudent to exclude populations at risk for neurocognitive deficits based on their underlying comorbidities (e.g., neurological, plastic, and reconstructional facial and cardiac defects).

Twin and Sibling Studies

To reduce the heterogeneity among children, parental education, and socioeconomic status, several studies focused on associations between the exposure of identical twins or siblings and subsequent neurocognitive deficits. The identical Twin Registry in the Netherlands yielded 1143 monozygotic twin pairs including 71 twins who were discordant for anesthesia and surgery before 3 years of age [165]. Standardized testing and teacher ratings of all the twin pairs showed significantly lower scores in those exposed to anesthesia compared with those who were not exposed. However, when the same scores were compared in twins who were discordant for anesthesia, they did not differ. This supported the notion that exposure to anesthesia at a young age may be a marker for a child's vulnerability to developing learning difficulties at a later date, but anesthesia per se does not substantively result in cognitive dysfunction. A major limitation of the study was the small sample size, the absence of details regarding the type of surgery, and the type of anesthesia and its duration.

In a retrospective sibling cohort study of children with New York Medicaid insurance, the incidence of developmental and behavioral disorders in 304 children <3 years of age who received anesthesia was compared with that in 10,146 unexposed children [166]. Disorders in children exposed to anesthesia were twice as frequent compared with those siblings who were unexposed. Furthermore, the risk of disorders in the exposed group was 1.1 after one anesthetic exposure, 2.9 after two exposures, and 4.0 after three or more exposures. When the 138 sibling pairs who were discordant for anesthesia were controlled for age, environmental, and in utero conditions, the matched relative risk for disorders was 0.9 [166].

In a recent and powerful sibling cohort design, 2346 sibling pairs were evaluated using the Early Development Instrument (EDI), a population-based measure of child development in five domains at ages 5–6 years [167]. (EDI is a validated 103 item teacher completed the assessment of development in the child in five domains: physical health, social competence, emotional maturity, language/cognitive development, and communication skills/general knowledge. Vulnerability was defined as a score below the tenth percentile in one of the domains.) In this study, development outcomes in exposed children did not increase compared with nonexposed biological siblings or in those siblings who were discordant for exposure to anesthesia. Importantly, all twin studies were mitigated for unmeasured biological vulnerability and home environmental influences on child development. These findings lend further support to the notion that a single exposure to anesthesia in early childhood is not associated with detectable adverse child development [167].

To investigate the effect of general anesthesia on the subsequent development of ADHD, the Swedish twin database extracted those twins who had been exposed to general anesthesia before the age of 12 years [168]. Of the 68 twins who were discordant for anesthesia, the association (1.02) between anesthetic exposure and ADHD was very weak. However, it should be noted that the children were not toddlers at the age of exposure but were as old as 12 years and 88% of the children received only a single anesthetic, reducing the power of the study.

Large Databases

To further clarify the impact of early exposure to general anesthesia on cognitive development in children, four large databases were searched; two studies were conducted in Canada [169, 170] and one each in Sweden [171], Australia [153, 154], and the UK [172].

In 2016, the EDI was measured in 3850 children who were exposed to a single anesthetic preschool and 620 who were exposed to 2 or more anesthetics, and both of these groups were compared with 13,586 matched but nonexposed children in Ontario, Canada [169]. Overall, the children's developmental vulnerability increased slightly based on the EDI metric in the exposed versus unexposed children, with an odds ratio (OR) of 1.05. In addition, the developmental vulnerability in children age > 2 years at the time of their first anesthetic was greater than in controls, OR 1.05. In contrast, developmental vulnerability after single and multiple anesthetic exposures at <2 years of age did not increase compared with controls [169]. These data indicate that although developmental vulnerability in preschool-age children who were exposed to general anesthesia is greater than in those

unexposed, the difference was quite small. Moreover, those children <2 years of age at the time of a single or multiple exposures were at no greater risk for developing cognitive defects.

In a second cohort study from Manitoba, 3850 children exposed to a single GA and 620 exposed to ≥2 GA were matched to 13,586 unexposed children, using the EDI as their outcome tool to quantify the children's developmental vulnerability [170]. Developmental vulnerability after either a single or multiple anesthetics at <2 years of age was not increased, whereas it was increased for those exposed to a single anesthetic between 2 and 4 years of age, with deficits noted in communication/general knowledge and language/cognition. However, developmental vulnerability after multiple exposures between 2 and 4 years of age was not increased [170].

In 2017, the largest and most robust retrospective cohort study used academic school grades and IQ test scores in 33,514 children (male to female ratio of 2:1) after single or multiple anesthetic exposures before 4 years of age (e.g., preschool) to compare with the same metrics in 159,619 age- and gender-matched controls [171]. The academic or cognitive performance on a population level demonstrated that general anesthesia reduced the school grade scores to a small extent, 0.41% (95% CI, 0.12%–0.70%), and IQ test scores, 0.97% (95% CI, 0.15%–1.78%), compared with unexposed children. Furthermore, the types of surgery yielded significant heterogeneity: children who underwent ear, nose, and throat procedures reported lower scores compared with those who underwent abdominal procedures. Children with chronic ear infections are known to suffer behavioral and learning difficulties rendering the effect of anesthesia on developing cognitive deficits difficult [155]. Those who underwent urological procedures reported higher school grades and IQ scores. Also, the differences in scores associated with sex, maternal education level, and month of birth during the same year (December versus January) were several orders of magnitude greater than the effect of exposure to anesthesia [171]. Cognitive scores were lower after multiple (>3) exposures to anesthesia, although these were smaller than the difference noted between the months of birth.

A cohort of 2868 pregnant women whose children were born between 1989 and 1992 was enrolled in the Western Australian Pregnancy Study (Raine) to evaluate the long-term effects of prenatal ultrasound [153]. All children underwent neuropsychiatric tests through the first 10 years after birth and at 13 and 16 years of age. The testing was comprised of four domains: language, cognition, behavior, and motor function. To test for the effects of anesthesia before the age of 3 years, exposed children were tested at 10 years of age. Males were twice as likely as females to undergo anesthesia. Long-term deficits in language and abstract reasoning were greater in those exposed to anesthesia (whether single or multiple exposures) compared with unexposed children, although other domains did not differ between the exposed and unexposed. Even within the language domain, higher-order language skills such as the clinical evaluation of language fundamentals and the Peabody Picture Vocabulary Test did not differ suggesting that not all aspects of language are affected by exposure to anesthesia [153]. This study has several limitations including the varied type of surgeries that were included (e.g., neurosurgery and cardiac surgery, surgeries known to adversely impact neurocognitive development). In addition, almost 25% of the children underwent myringotomies and tubes that required a general, albeit brief, anesthetic (< 15 min), although chronic hearing loss is a recognized primary source of poor language development and learning problems [155]. Moreover, multiple paired comparisons introduced a possible Type 1 statistical error that remained unaccounted for.

The most recent longitudinal, cohort study comprised 13,433 children from the UK who were exposed to general anesthesia before 4 years of age and were evaluated for cognitive and behavioral development between 7 and 16 years of age [172]. After adjusting for confounding variables, no neurocognitive deficits in terms of cognitive ability, memory, attention, reading, spelling, and behavior difficulties on national exam performance were identified to be either clinically or statistically significant, although motor and social linguistic performance were significantly lower in the exposed group, worse after multiple anesthetics. The authors issued a cautious reassurance that exposure to general anesthesia does not seriously impact global neurodevelopment with the two exceptions above noted [172].

Prospective Human Trials

The General Anesthesia vs. Spinal (GAS) study was an international prospective randomized controlled trial that compared the Bayley III Scales of Infant and Toddler Development evaluated at 2 and 5 years after either a 1-h sevoflurane anesthetic or spinal anesthesia in infants undergoing inguinal hernia repair. At both follow-up ages, the Bailey Scales were similar [173, 174]. The proportion of with the number of participants The GAS study provides the strongest available evidence to date that approximately 1 h of a single anesthetic (sevoflurane) exposure in early life is safe and does not lead to cognitive dysfunction in either the short or long term. Limitations of this prospective study included the brevity of the anesthetic exposure, the limited exposure to a single pro-apoptotic anesthetic, the absence of repeated exposures to sevoflurane, and the proportion of participants in both groups

who were lost to follow up, 30 and 42%, using an ITT or APP approach, respectively.

The Pediatric Anesthesia Neurodevelopment Assessment (PANDA) trial was an ambidirectional cohort study that compared the neurocognitive and behavioral outcomes from 105 healthy sibling pairs who were discordant for exposure to anesthesia before the age of 3 years [175].

Neurocognitive and behavioral outcomes were collected prospectively, although the data on the anesthetic exposure were collected retrospectively. The primary outcome, global cognitive function (IQ) at age 8–15 years, did not differ between siblings. Secondary outcomes including domain-specific neurocognitive functions and behavior also did not differ between siblings [175].

The Mayo Anesthesia Safety in Kids (MASK) study, a second ambidirectional study, compared a matched cohort study of 997 children who were unexposed, singly exposed, or multiply exposed to general anesthesia before 3 years of age based on their medical charts [176]. These children underwent comprehensive late neuropsychological testing at ages 8–12 years or 15–20 years. The primary outcome measure, the Full-Scale Intelligence Quotient Standard Score of the Wechsler Abbreviated Score of Intelligence, was similar among the unexposed, singly exposed, and multiply exposed children [176].

Using the data from the MASK study, the same cohort of children was reanalyzed using the Operant Test Battery (OTB)—the battery of tests used to investigate deficits in infant macaque monkeys after anesthesia [177]. In the primary analysis, there was no association between exposure to anesthesia and neurocognitive deficits after correcting for multiple comparisons. In this exploratory factor analysis, the OTB scores loaded onto four factors, and the score for one factor was significantly less in multiply exposed children, but significance did not survive a sensitivity analysis accounting for outlying values.

The TREX (Trial Remifentanil and dEXmedetomidine) pilot study is a multicenter study that assessed an alternative anesthetic technique for infants (1–12 months) undergoing lower abdominal/lower extremity surgical procedures that were expected to last for more than 2 h. The protocol specified an inhalational induction with sevoflurane, a caudal block, and maintenance of anesthesia using both remifentanil and dexmedetomidine infusions. The pilot study reported that 87.5% of the 56 infants achieved a satisfactory depth of anesthesia. Based on the pilot study, this anesthetic prescription seemed to be potentially beneficial for infants undergoing surgery as it reduced the time the infants would be exposed to inhaled anesthetics [178]. This pilot study laid the groundwork for subsequent studies that will investigate alternative anesthetic regimens to minimize infant's exposure to proapoptotic drugs.

Relevant Human Outcome Measures, Population Migration, and Sample Sizes

It must be emphasized that the potential phenotype of anesthesia-related neurotoxicity in young children is unknown [156, 164]. But if such a phenotype exists, it is essential to ascertain a meaningful outcome metric for the possible effects of anesthesia on cognitive function in humans including when and how to best evaluate the child. Current crude outcome measures such as developmental disorders in preschool, learning disabilities (LD) in elementary school, attention-deficit hyperactivity disorder (ADHD), social disturbances in adolescence, psychiatric disorders in adulthood, loss of various cognitive functions, or early dementia in the elderly are influenced by a multitude of factors. Large population studies identify associations but cannot identify causality. More importantly, it also remains to be established how well a single short-term interim outcome metric performed in early childhood or adolescence adequately predicts the outcome later in life. Extensive and repeated neurodevelopmental testing may be more likely to identify any potential phenotype (e.g., abnormalities in speech and language neurocognitive impairment) [156]. Importantly, it is unknown under what circumstances repeated individual cognitive testing is meaningful human outcome measures. Assessment of academic performances has a pragmatic advantage as an outcome measure in that parents are likely to be more interested in their child's academic standing in school [179] and importantly good academic achievements require good speech and language skills [180].

The use of ADHD as an outcome measure for anesthesia-related neurotoxicity requires further evaluation [152] as the diagnosis and treatment of this disorder are contentious [157]. ADHD is afflicted by ascertainment bias as demonstrated by the large variation in its prevalence among countries, states, races, sexes, and ethnicities. In 2011, two million more children were diagnosed with ADHD in the USA compared with 2003, with one in five adolescent males in the USA labeled with ADHD. More than two-thirds of these children were prescribed long-term medication such as dexamphetamine [181, 182]. Additionally, ADHD is associated with an array of psychiatric disorders and LD. For these reasons, ADHD seems to be of limited value as an outcome measure for anesthesia-related neurotoxicity. Autism spectrum disorder has also served as an outcome measure in anesthesia-related neurotoxicity studies [158] with similar arguments as those mentioned for ADHD applied to question the validity of this outcome measure. In the case of autism, it is important to appreciate that it affects up to 1% of children, beginning in early childhood or later and progressing throughout adulthood.

The degree of migration of study subjects is of major concern in many of the human cohort studies [151, 152, 183]. Therefore, sufficiently large sample sizes are required to detect even modest associations of perioperative factors that impact neurocognitive outcomes. Too many studies included small cohorts that limited the power of the studies to identify differences and associations. Multiple (individual) testing has also been employed to compensate for this; however, this approach introduces the risk of Type 1 statistical error, particularly considering that many of such tests are interrelated [180].

Age at Exposure, Duration of Surgery/Number of Exposures, and Impact of Surgery

Neurogenesis in infants and children peaks at different ages within brain regions [28, 184]. Surprisingly, neurogenesis continues in some regions (e.g., dentate gyrus and olfactory bulb) into adulthood far beyond the previously suggested window of vulnerability [20, 28]. The belief that the youngest and most immature infants are at the greatest risk of anesthetic agent-induced neurotoxicity is not reflected in the currently available human studies [143, 144, 146, 169–171, 185]. In a summary of the neurocognitive sequelae after exposure to anesthesia in infants and children by age, there were no age-associated changes in either the severity or nature of the neurocognitive defects identified [186].

In 2016, the FDA in the USA issued a notice cautioning that prolonged anesthetic exposure may increase the risk of long-term cognitive dysfunction, without defining the term "prolonged." This was based primarily on animal data. The very few studies that focused on prolonged exposures and procedures suggest that confounding variables other than the mere exposure to anesthetic agents may be critical in developing cognitive dysfunction [149, 187]. However, a recent cohort of 212 children who were more than 5 years after being diagnosed with acute lymphoblastic leukemia for which they received 5699 anesthetics demonstrated different results [188]. The cohort underwent a comprehensive battery of neurocognitive tests after 8 years of age to determine the neurocognitive and neuroradiological effects of multiple anesthetics over a prolonged period. After adjusting for confounders, the authors determined that increasing cumulative exposure to and duration of propofol or isoflurane anesthesia resulted in neurocognitive impairment and neuroradiological abnormalities beyond those associated with the chemotherapies. This small but focused sample of cancer survivors raises concerns about the effects of exposure to a large dose of anesthetics over a prolonged period in chronically ill children, and the authors rightly caution that we minimize the dose and duration of exposures to anesthetics in such children [188]. Limitations of this study included the absence of baseline measurements due to the urgent need to commence cancer treatment. Importantly, the sicker a child with cancer is, the more likely he/she is to require repeated anesthesia. As a final thought, anesthesia was required in this study and will be required in the future in analogous situations if we are to ethically and successfully treat cancer in children.

To further understand the magnitude of the impact of the FDA warning regarding prolonged anesthesia in children, a retrospective review of 1.5 million anesthetics from the National Anesthesia Clinical Outcomes Registry reported the duration of anesthesia in children undergoing elective surgery. The authors reported that the median duration of anesthesia was <1 h in all age groups except those <1 year for whom the median duration was 79 min (upper 90th %ile was 210 min) and 13–18 years for whom it was 70 min (upper 90th %ile was 170 min) [189]. Overall, 94% of the anesthetics were ~ 1 h in duration. Only 6% of the anesthetics fell into the category considered "prolonged" by the FDA. Using a much smaller database from a tertiary referral center in the USA, the authors reported that less than 4% of the anesthetics administered to young children that exceeded >3 h in duration were multiple exposures before 3 years of age or both [190]. Children who require prolonged anesthetics almost certainly had illnesses that require repeat anesthetics to treat or cure the underlying illness or required surgery of prolonged duration to remove a tumor or treat some other potentially life-threatening condition. In those small numbers of children with chronic diseases who require prolonged exposures to anesthesia, clinicians should design their anesthetic prescriptions to minimize the duration, number, and/or dose of proapoptotic anesthetics and include non-apoptotic strategies including regional anesthesia where possible to minimize the risk of neurocognitive deficits.

The effects of surgery including the stress response, pain, and neuroinflammation cannot be disentangled from that of the anesthetic agent itself [191], with inconsistent results from two studies of the effects of pain on neurocognitive deficits in rodents [135, 136]. Both surgery and underlying pathology independently influence the subsequent neurocognitive outcome. The single most important cofactor may be the effects of surgery. The impact of stress responses, nociception, and neuroinflammation on (long-term) neurocognitive function requires further exploration [149, 187, 191].

Sex, Parenting, and Low Birth Weight

Another factor that may confound the long-term neurodevelopment is sex. Male sex can influence the need for surgery, as inguinal hernia repair and pyloromyotomy are far more common in males than females [25, 29]. Sex is known

to independently impact the neurobehavioral outcome [192, 193]. Evidence from PND7 rats indicates that when males and females were exposed to isoflurane, apoptosis and simple object recognition were similarly affected at PND38, although social memory and object recognition in novel locations in the males were impaired compared with females [193].

Maternal age and, more importantly, higher socioeconomic status are strongly associated with better neurobehavioral outcomes and with enhanced capacity to recover from any injury. Of note, the level of parental education is more important than parental occupation and socioeconomic status as these are subject to changes over time, whereas, after the age of 30 years, the level of parental education rarely changes [194]. Low birth weight (prematurity) is strongly associated with negative neurobehavioral outcomes as are other comorbidities such as congenital defects [195].

Future Studies

Unmeasured confounding factors limit large observational retrospective cohort studies. For example, the effects of sleep duration, relationships with peers, and levels of physical activity are difficult to disentangle from the exposure to anesthesia when using academic performance as the only outcome measure of cognitive dysfunction. Furthermore, given that multiple metrics have been used to assess development, cognition, intelligence, academic achievement, and neuropsychological diagnoses, our ability to merge and collate the results of the studies has become increasingly challenging [60]. Future observational studies will only yield meaningful results if they are sufficiently powered, include infants and children with comparable surgeries, comorbidities, indication for exposure, follow up and consistent outcome metrics [165]. Several questions need to be answered if we are to unravel the true effect of general anesthetics on vulnerable young infants and children (Table 18.4). Large international, randomized controlled trials with standardized outcome measures are needed to discover possible associations between prolonged anesthesia or multiple anesthetics and adverse neurocognitive outcomes, although they face insurmountable obstacles: an enormous commitment of time, substantive budget, and an international cooperative of pediatric centers.

Table 18.4 Further questions that should be answered in future clinical research

Is there a particular phenotype of the patient that is at risk of neurotoxicity?
Are there periods of significant vulnerability to neurotoxicity, and if so when are these?
Which anesthetic agents confer the most harmful effects and at what dose range?
Are short multiple exposures, for example, staged procedures, safer than one long exposure?
Is there a dose-response curve?
Which outcome measures are most affected by neurotoxicity if any?

Other Aspects

Many other perioperative factors may impact later neurodevelopment and may affect the neurodevelopment to a much larger extent than anesthetic exposure early in the child's young life [196]. These include a series of (small) physiological, metabolic, and biochemical factors induced by general anesthetics and surgery that are known to impact survival and morbidity [197]. Likely, the aggregate of several relatively small and consistent improvements in clinical care may very well substantively influence the overall outcome ("aggregation of marginal gains") [3].

The conduct of anesthesia by skilled practitioners in an appropriate pediatric environment supported by sufficient resources will improve the overall perioperative care for infants and children. For example, it is crucial to maintain normal physiological and metabolic indices including oxygenation, normo-capnia, normo-natremia, blood pressure within the normal limits, euglycemia, and normo-thermia and to minimize fear and anxiety. These are listed in the safe-tots.org initiative as the 10 N model for safe anesthesia (Fig. 18.2) [197]. Although deviations in physiologic variables have not been directly linked to neurocognitive deficits, ensuring physiologic homeostasis in the neonates eliminates confounding variables from being implicated should neurocognitive deficits occur. In the European Apricot study of clinical morbidity in pediatric anesthesia, neonates experienced the greatest frequency of critical cardiovascular and respiratory adverse events, the age group at great risk for neurocognitive deficits due to rapid synaptogenesis [198]. In a retrospective case series of seven infants who underwent relatively minor surgery at a major pediatric institution, all seven developed postoperative encephalopathy (including seizures) that appeared to be consistent with cerebral hypoperfusion [199]. During the anesthetic, hypotension was observed in the majority, only one was given glucose intraoperatively, and two-thirds exhibited mild hypocapnia. How each or all of these physiologic deviations possibly contributed to the neuropathology remains unclear. Hypotension has been reported previously in neonates and infants under general anesthesia and is known to occur more frequently in neonates than older children, although the definition of hypotension in infancy remains elusive and ill-defined [200–203]. In the European Nectarine study of morbidity in neonatal anesthesia, 35% of neonates and infants <60 days postnatal age experienced either hypotension or hypoxemia ($SpO_2 < 85\%$) during general anesthesia [204]. In a review of

Fig. 18.2 Maintenance of physiological homeostasis is key for the safe conduct of anesthesia in children, as stated by the safetots.org initiative (www.safetots.org)

infants undergoing pyloromyotomy, hypotension was common particularly in preterm infants and in neonates [205], and desaturation occurred in 18–30% postintubation depending on the type of rapid sequence induction that was used [206]. Strict maintenance of these physiological variables may be aided by advances in monitoring technology such as near-infrared spectroscopy (NIRS) allowing regional perfusion and oxygenation to be continuously assessed and maintained throughout prolonged exposure to anesthesia. In addition, the conduct of anesthesia by skilled practitioners in an appropriate pediatric environment supported by sufficient resources also needs to be addressed. The important questions of *who*, *where*, *when*, and *how* young infants and children should be anesthetized will need to be addressed. For more information and further updates about these issues, the readers are referred to www.safetots.org [197].

Finally, concerns about the long-term neurocognitive outcomes after surgery and anesthesia in early life are further complicated by several environmental factors that are potentially hazardous to the neurodevelopment of children. Of particular concerns are the effects of chronic exposure to lead, methylmercury, pesticides, perfluorinated compounds, fluoride, and phthalates, to name a few [207], and poverty and low socioeconomic status [208].

Important Issues to Consider

With conflicting evidence regarding the effects of exposure to anesthetic agents on neurodevelopment in humans, clinicians face an ethical dilemma: *how*, *when*, *if,* and *to what extent* these issues should be discussed during the consent procedure with parents and caregivers? Knowing there is a panoply of factors that may affect a child's neurodevelopment, it is daunting to quantify the impact of exposure to anesthesia on an individual child's neurodevelopment, given that anesthesia is required on compassionate grounds to facilitate surgical and diagnostic procedures in young children. In some institutions, pamphlets are available in surgeon's offices and in clinics that address the issue of anesthesia and its possible effects on the neurodevelopment of children. Would such a discussion at an inopportune time (as anesthesiologists often are given) immediately before surgery garner excessive concerns for parents when there are

few or no alternatives? If the parents raise direct questions regarding the risks of anesthesia on neurocognitive outcomes in their child, then the questions should be answered in an honest and forthright manner. Since most children who present for surgery are healthy, the risk of neurocognitive adverse outcomes after a single brief anesthetic is exceedingly small. However, if the child presents with multiple comorbidities or has experienced multiple anesthetics, the perioperative experience may increase the risk of neurocognitive adverse effects, although it is far more important to reassure the parents that their pediatric anesthesiologist is experienced and will deliver a "first-class anesthetic" maintaining vital signs within normal limits to optimize their child's outcome and minimize their perioperative risks. If the parents are vacillating over delaying surgery until their child is older, it is important to remind them that this decision should not be taken lightly; the parents or legal guardians should be fully aware of and understand that the risks of delaying surgery or a medical procedure that may introduce undesired sequelae must be balanced against the biologically plausible, but currently unknown, risk of neurotoxicity in the child.

It should be noted that the neurocognitive outcome studies from both Europe and North America varied in the metrics they used to assess long-term cognitive function, which may explain discrepant results among studies. Although big data epidemiological studies yielded tenuous associations between anesthetic exposure and neurocognitive deficits [169–171], they serve to identify associations, not causations, between the variables. Since clinicians on both continents use similar anesthetic regimens and techniques and perform similar surgeries on children with similar disease processes, the fact that studies in one region reported positive associations whereas those in the second region did not raises several possible explanations for the discrepancy including that the neurocognitive outcome metrics in one region were less sensitive than those in the other regional and/or that the general provision of healthcare, specialist care, standards of anesthesia care, and, most importantly, education and support differed resulting in the conflicting outcomes [209].

The history of anesthesia-induced apoptosis and neurocognitive dysfunction differs from other serious issues that anesthesiologists have confronted previously. Such issues were primarily clinical dilemmas and unexpected morbidity and mortality that spurred extensive research to understand and resolve. Examples of these include halothane hepatitis, malignant hyperpyrexia, methoxyflurane-induced renal failure, and rapacuronium pulmonary complications and death. However, in the case of anesthetic-associated cognitive dysfunction, it was discovered first by serendipity in animals, [1, 18] not humans. This spurred basic (animal and laboratory) science research to elucidate the putative agents and the plausible cellular mechanisms for anesthetics to cause the observed pathology. The research focused on anesthetic neurotoxicity ($GABA_A$, NMDA receptors) during periods of rapid synaptogenesis, attracting generous funding, academic merit, and publicity (https://www.smarttots.org). Interestingly, attention to improving the safe conduct of general anesthesia (by maintaining blood pressure, $PaCO_2$, electrolytes, temperature, and blood glucose concentration within physiologic norms) in the vulnerable infant and child remained largely neglected and ignored. Although it is common knowledge that the risk for perioperative morbidity in infants and children particularly by inexperienced pediatric anesthesiologists is not insignificant, several national anesthesia societies were unwilling initially to accept and/or pursue specialized certification of pediatric anesthesiologists. Subspecialty training in pediatric anesthesiology is available in many regions, although in many other regions, standardized pediatric anesthesia certification remains elusive [210].

As outlined above, prospective studies and worldwide collaborations such as the PANDA, MASK, and GAS studies have focused on the need for excellence in perioperative quality of care [173–177]. The plausible negative effects of the anesthetic agent on neurodevelopmental outcomes have highlighted the importance of the safe conduct of anesthesia to minimize perioperative critical events and improve outcomes [199, 211, 212]. In addition, the safetots.org initiative has galvanized global support from experts in pediatric anesthesia. Although it remains important to continue to investigate anesthetic-related neurotoxicity, we should not lose sight of the need to guarantee the delivery of high-quality and consistently safe anesthesia to neonates, infants, and children at all times.

Conclusion

There is incontrovertible evidence that general anesthetics adversely affect newborn animals from rodents to subhuman primates both histologically and neurocognitively. These effects become apparent in the early postexposure period and persist as the animals mature to adulthood. The quintessential question is how does this evidence translate into the vulnerable human?

It has proven difficult to find a human correlate to the animal model that demonstrated anesthesia-related neurotoxicity in the developing brain (Table 18.5). In the only prospective, controlled, randomized study that exposed young infants and children to ~1 h of a single anesthetic, sevoflurane, for inguinal hernia repair, neurobehavioral deficits 5 years after exposure were similar to those in a matched cohort who received only regional anesthesia for the same surgery [174]. Weaker evidence suggests that repeated exposures to anesthesia and surgery may be associated with mar-

Table 18.5 Further questions that should be answered in future clinical research

• General anesthesia is neurotoxic to the developing brain in vulnerable animals, resulting in short-term and long-term neurocognitive impairment. Translating these animal data into a human context presents enormous challenges
• A single, brief general anesthetic is not harmful to young children. Recent large-scale observational studies found minimal neurocognitive impairment after anesthesia and surgery
• The recent FDA warning regarding potential harm to fetuses and children <3 years who require prolonged (>3 h) or multiple anesthetic exposures was based on nonhuman research. Fewer than 6% of children require prolonged exposure and/or frequent anesthetics; these children most likely have chronic diseases that themselves may predispose to long-term cognitive defects that may preclude distinguishing the effects of anesthetics from the chronic disease
• Environmental, social, biological, and perioperative factors other than anesthetic drugs are far more important determinants to ensure intact neurocognition later in life
• There is currently no need to change anesthetic clinical practice and no need to postpone or cancel procedural or surgical interventions

ginally poorer outcomes based on neurocognitive indices such as LD and ADHD, although neonates and young infants do not appear to be at greater risk for neurocognitive dysfunction than older children. Nonetheless, chronically ill children who require multiple or prolonged surgeries may be at risk for neurocognitive dysfunction beyond that associated with the underlying disease process. Perioperative factors such as poor nutrition, chronic hypoxia, and hypotension may impact neurocognitive outcomes to a greater extent than anesthetic/surgical exposures themselves, but this may prove difficult to confirm in clinical studies. Subjecting neonates and young children to invasive procedures and surgery without the full benefits of anesthesia and analgesia is both ethically unacceptable and morally reprehensible, even if the risk of an adverse occurring is small. The authors together with the editor believe that when all of the available evidence is considered in aggregate, neither the current practice of pediatric anesthesia nor the timing of procedures and surgery should be postponed or canceled to reduce the risk of potential neurotoxicity.

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Neonatal Resuscitation for Anesthesiologists

19

Satyan Lakshminrusimha and Payam Vali

Key Points for Neonatal Life Support in the Delivery Room (Fig. 19.1)

- **R**isk factors—Review maternal and fetal risk factors; anticipate and prepare.
- **E**valuation—Ongoing assessment.
- **S**kin-to-skin contact with mothers can help with temperature management.
- **U**mbilical cord management—Deferring cord clamping for >30 s.
- **S**pO_2 monitoring is used to guide oxygen therapy if needed.
- **C**ardiac monitoring (preferably with EKG if extensive resuscitation is needed)—increasing heart rate is the most important indicator of response to resuscitative interventions.
- **I**nflation and ventilation of the lungs are a priority for infants who need support.
- **T**horacic (chest) compressions if poor response to positive pressure ventilation (PPV).
- **A**drenaline/epinephrine—IV reasonable if poor response to chest compressions.
- **T**ension pneumothorax—Rule out if poor response to adrenaline.
- **E**xpand volume with normal saline or blood if history or exam is consistent with blood loss.
- **D**irection of care—Discuss with family and team if no response by 20 min.

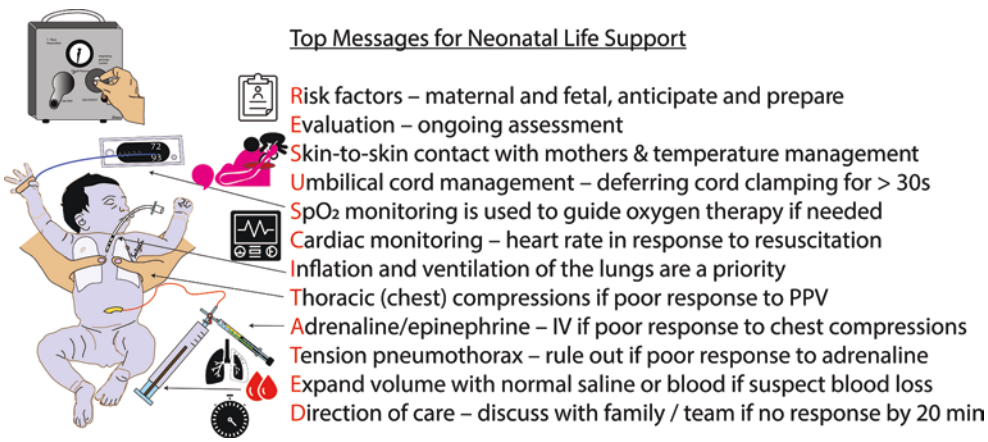

Fig. 19.1 Twelve key points to remember during neonatal resuscitation. Based on Aziz et al. [18]. Mnemonic—RESUSCITATED Copyright Satyan Lakshminrusimha

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Introduction

Anesthesiologists are often called to help in neonatal resuscitation. These situations may include (i) in the delivery room (DR) when an infant is born unexpectedly depressed, (ii) emergent delivery when the neonatal team has not arrived, (iii) when the neonatal or obstetric team has difficulty in resuscitation and needs help, and (iv) during code situations in the operating room. Anesthesiologists are experts in airway management and resuscitation. However, when the anesthesiologists are resuscitating a neonate, it would be good to be aware of the basic principles of the neonatal resuscitation program (NRP) established by the American Academy of Pediatrics (AAP) and the American Heart Association (AHA) [1] so that there is synchrony with the participating neonatal and pediatric resuscitators [2].

Equipment

As delivery may occur in situations and locations that are not completely organized for resuscitation of a newly born infant, a quick equipment and personnel checklist as shown in Fig. 19.2 is beneficial.

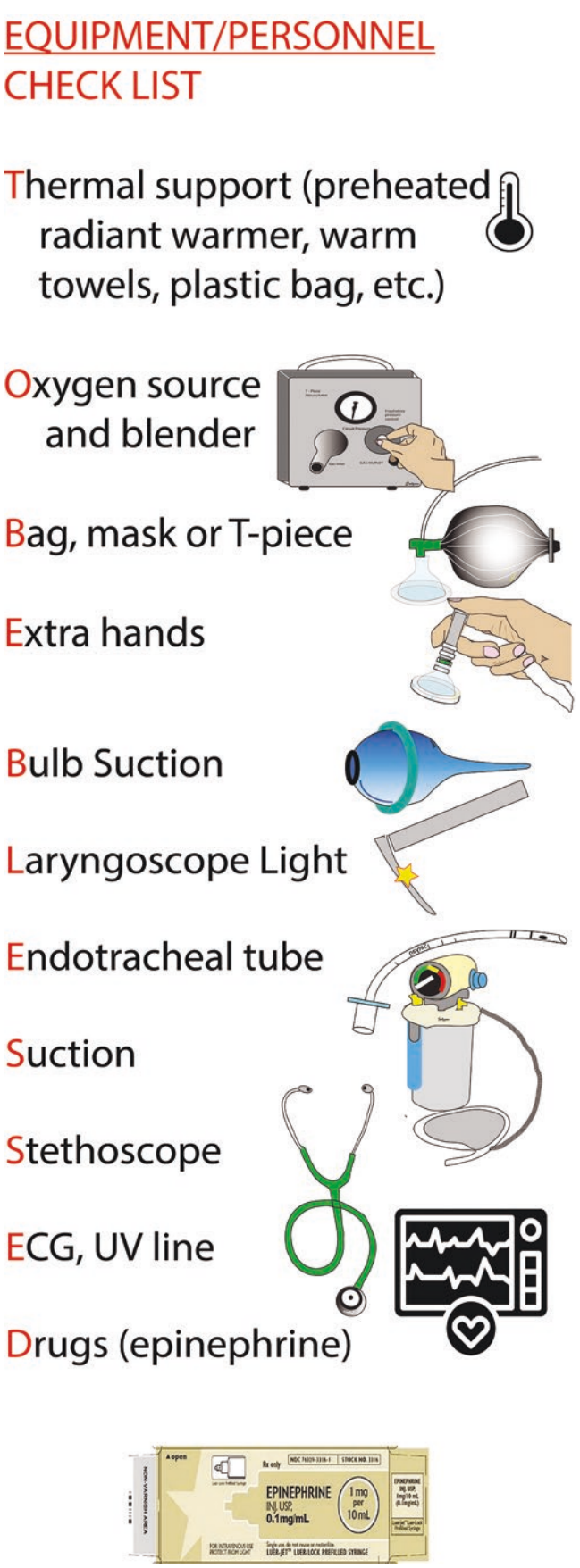


Fig. 19.2 Equipment and personnel checklist before neonatal resuscitation at delivery. Every birth is TO BE BLESSED is a mnemonic for this checklist. Copyright Satyan Lakshminrusimha

Physiology of Transition at Birth (Fig. 19.3)

Fetal Circulation (Fig. 19.3a)

The fetus depends on the maternal circulation for gas exchange [3]. The fetal lung is filled with liquid. It has a small blood flow that does not participate in gas exchange. Pulmonary vascular resistance (PVR) is high due to hypoxic pulmonary vasoconstriction. The pulmonary arterial blood is diverted across the ductus arteriosus (DA) to the placenta. Oxygenated blood from the umbilical vein streams across the right atrium through the foramen ovale (FO) to the left atrium and supplies the coronary and cerebral circulation. Although the fetal PaO_2 is low (~ 25 mm Hg), it compensates through four mechanisms: (i) presence of fetal hemoglobin (HbF) with strong oxygen affinity, (ii) large ventricular blood flow (combined ventricular output of ~450 mL/kg/min as compared with 150 mL/kg/min in an adult), (iii) diverting more oxygenated blood to the brain and heart (preductal), and (iv) increased hemoglobin values (15–19 g/dL in term neonates) [3–5].

Transition at Birth and Deferred Cord Clamping (DCC)

As the infant is born and cries, air enters the alveoli increasing the partial pressure of alveolar oxygen (PAO_2) leading to a decrease in PVR and pulmonary vasodilation. Consequently, pulmonary venous return increases (Fig. 19.3b) and contributes to increasing the left ventricular preload. During this process, deferring umbilical cord clamping (DCC) until respiration becomes established (physiological cord clamping) will provide umbilical venous flow as a source of left ventricular preload as pulmonary venous flow is gradually increasing. DCC for at least 30–60 s is recommended in all births where immediate resuscitation is not required [6].

Once the umbilical cord is clamped, due to removal of the low-resistance placental circuit, systemic vascular resistance (SVR) increases. An increase in SVR/PVR ratio leads to reversal of shunts across the DA and FO from right-to-left (pulmonary to systemic) to left-to-right (systemic to pulmonary; Fig. 19.3c). These shunts contribute to a rapid and eight- to tenfold increase in pulmonary blood flow after birth.

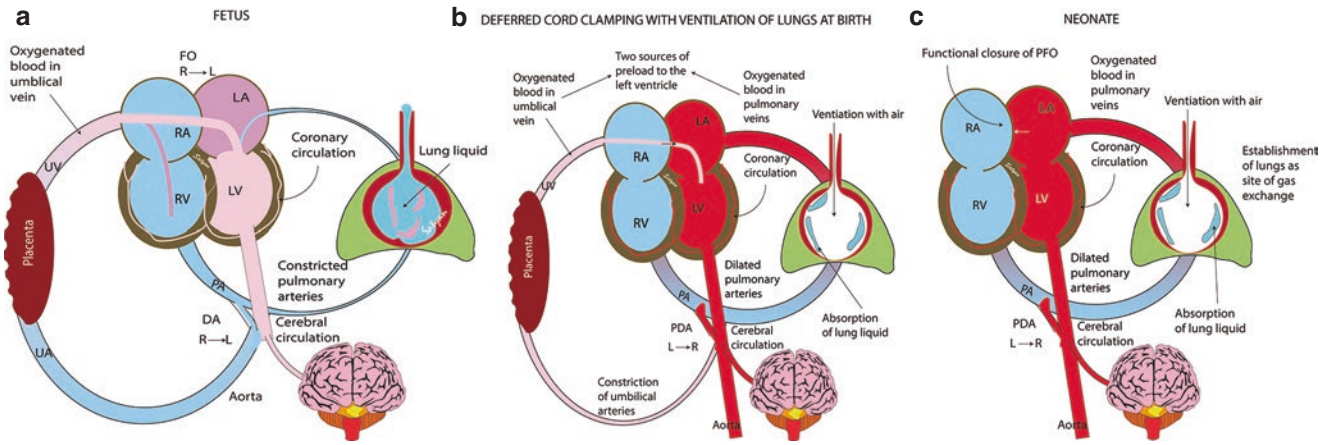


Fig. 19.3 Transition from fetal to neonatal physiology. (**a**) Fetal circulation with liquid filled lungs. The placenta serves as the organ of gas exchange with deoxygenated blood coming from the umbilical arteries (UA) and oxygenated blood leaving the placenta to the fetus through the umbilical vein (UV). Oxygenated blood enters the right atrium (RA) and crosses through the foramen ovale (FO) right-to-left (R → L) to perfuse the cerebral and coronary circulations. Deoxygenated blood from the systemic veins enters the RA and the right ventricle (RV) to the pulmonary artery (PA). As the pulmonary vasculature is constricted with high resistance, blood enters the aorta through the ductus arteriosus (DA) and reaches the placenta. (**b**) Transitional circulation during deferred (physiological) cord clamping. Oxygenated blood from the umbilical vein and the pulmonary veins (by oxygenation through the newly ventilated lungs) enters the left atrium and contributes to the left ventricular (LV) preload. (**c**) Neonatal circulation after removal of the placenta is characterized by reduced pulmonary vascular resistance (due to ventilation of the lungs) and increased systemic vascular resistance (due to removal of the placenta) resulting in a left-to-right (L → R) shunt at the patent ductus arteriosus (PDA) and eventual closure of the PDA and patent foramen ovale (PFO). Ventilation of the lungs is the key step in this transition. Lungs are established as the site of gas exchange. (Modified from Maheshwari Evidence Based Neonatology, Copyright Satyan Lakshminrusimha)

Asphyxia

Classic studies by Dawes et al. have described the course of respiratory and hemodynamic changes that occur with fetal asphyxia (Fig. 19.4) [7]. Soon after fetal asphyxiation, there is an increase in respiratory rate, heart rate, and blood pressure followed by primary apnea. If there is prompt intervention with stimulation, respiratory effort can improve during primary apnea. However, if the asphyxial insult continues, the fetus suffers from secondary apnea and will require positive pressure ventilation (PPV) to recover. During secondary apnea, hypotension and bradycardia occur, and if asphyxia persists, cardiac arrest follows necessitating circulatory support with chest compressions.

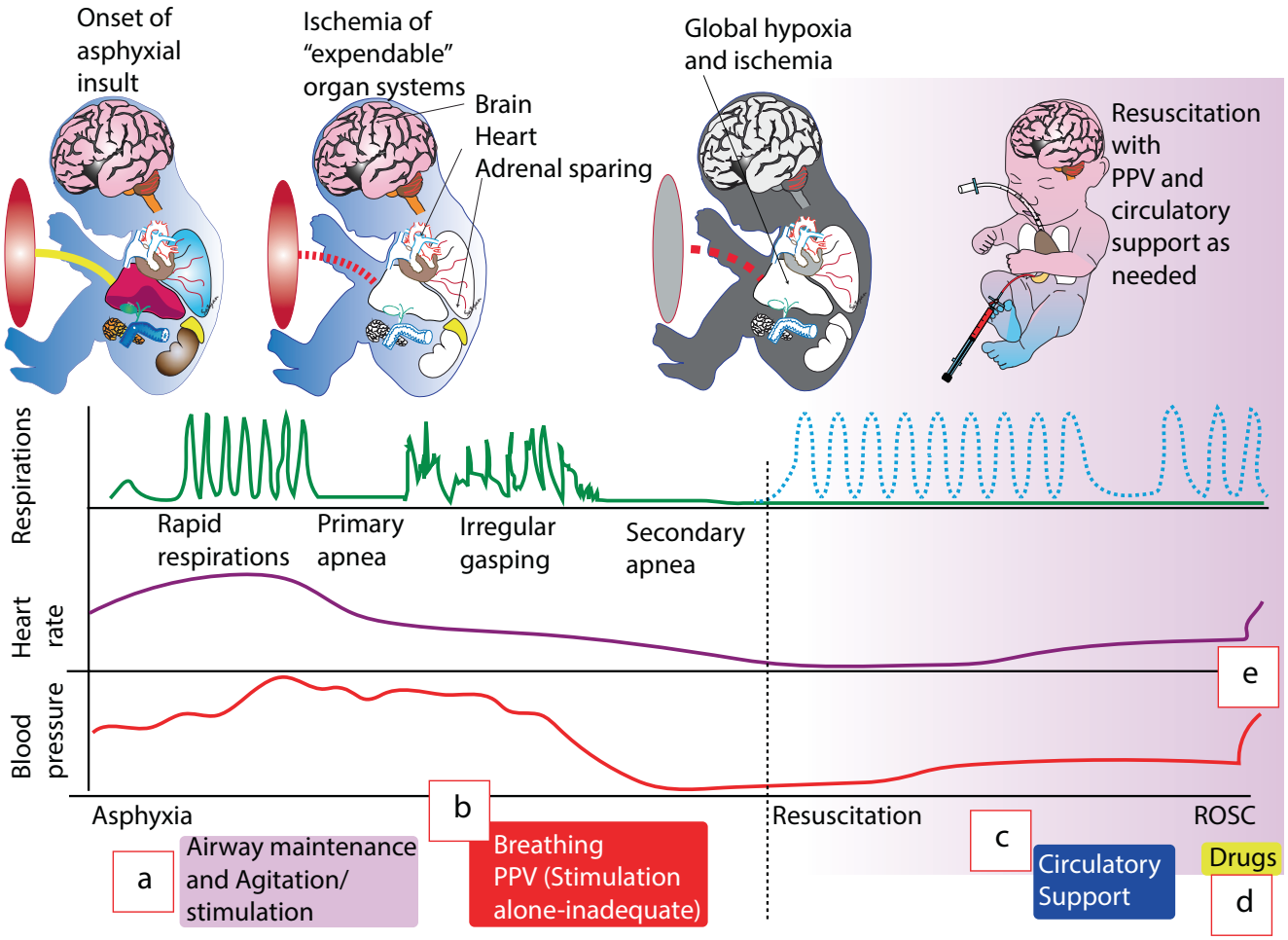


Fig. 19.4 Pathophysiology of asphyxia and resuscitation showing respiratory rate (green line), heart rate (purple line), and systemic blood pressure (red line). Soon after an asphyxial insult, rapid respirations are observed as a compensatory phenomenon. Subsequently, primary apnea associated with bradycardia is noted. At this phase, blood flow to nonexpendable organs such as the brain, heart, and adrenals is preserved, and blood pressure remains within normal limits. (**a**) Maintaining the airway and agitation (stimulation) is required at this stage. However, if stimulation is not provided or if asphyxial insult is severe and ongoing, irregular gasping followed by secondary apnea and hypotension occur. (**b**) Breathing with positive pressure ventilation (PPV) is required in the presence of secondary apnea as global ischemia can deprive blood flow to the brain and heart. The hyphenated blue line overlapping respirations depicts PPV. (**c**) Circulatory support in the form of chest compressions is necessary in the presence of persistent bradycardia in spite of effective PPV. (**d**) Drugs—epinephrine (or volume)—are indicated when PPV and chest compressions are ineffective. (**e**) Effective resuscitation results in return of spontaneous circulation (ROSC). (Modified from Maheshwari Evidence Based Neonatology, Copyright Satyan Lakshminrusimha)

Physiology of Resuscitation

The key step during neonatal resuscitation is effective ventilation of the lungs. During assessment, increasing heart rate is the best sign of response to resuscitation [2]. The steps of resuscitation include clearing the airway and stimulation for primary apnea, PPV for secondary apnea, and chest compressions and epinephrine for circulatory collapse (Fig. 19.4).

Preparation for Delivery

The anesthesiologist has primary responsibility for the mother. It is important to anticipate the need for neonatal resuscitation using the mnemonic GRASP by posing five questions (Fig. 19.5).

Gestational age—What is the expected gestational age?

Risk factors—Are there any additional risk factors (e.g., diabetes, hypertension, preeclampsia, and obesity)?

Amniotic fluid—Is the amniotic fluid clear? Presence of meconium or blood can be associated with the need for resuscitation.

Single/multiple—How many babies are expected?

Placental transfusion—Are there any plans for delayed cord clamping or cord milking? Factors that influence placental transfusion are shown in Fig. 19.6. With an intact cord, maternal blood gases and some anesthetic agents will continue to cross the placenta and reach the fetus/neonatal infant.

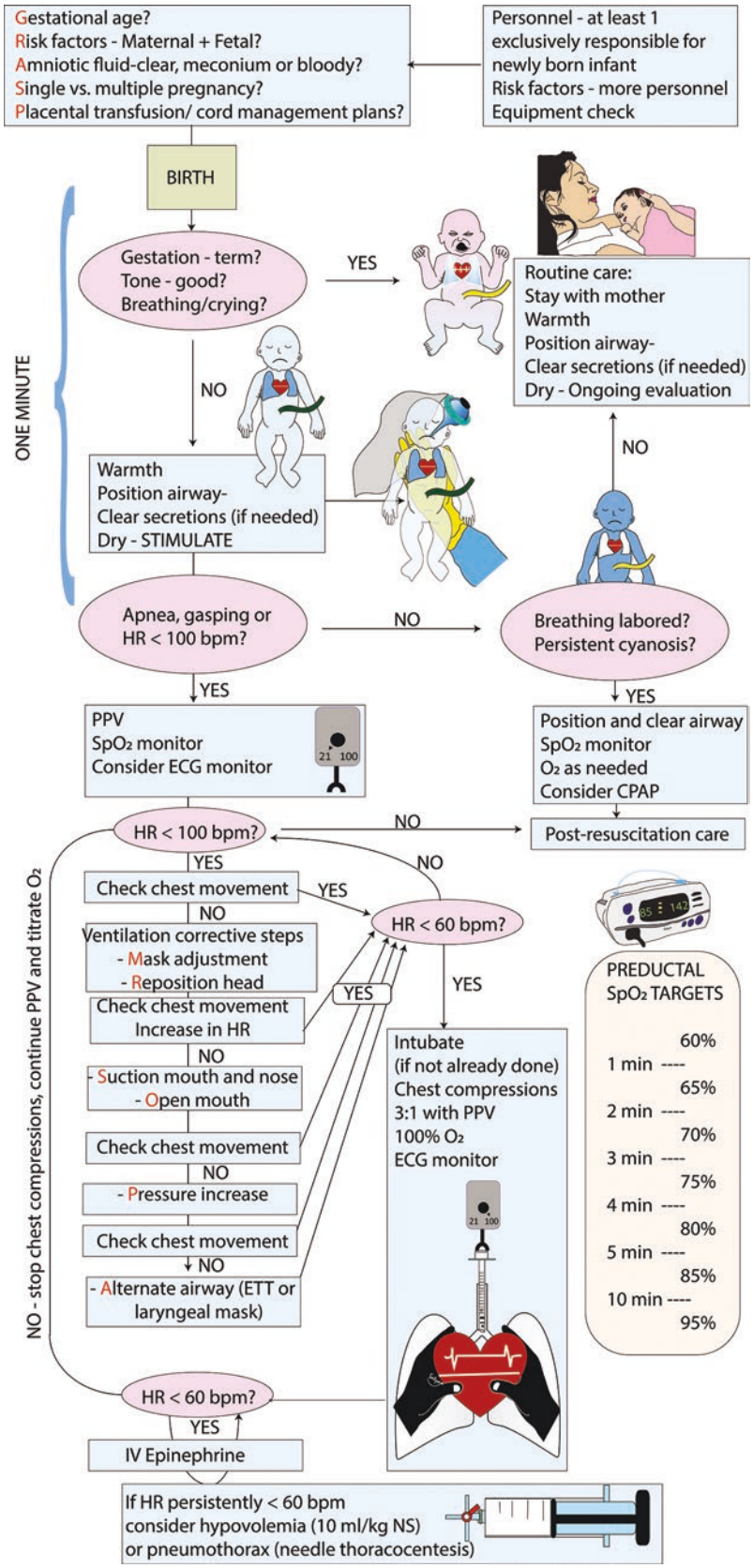


Fig. 19.5 Pictorial flow diagram of neonatal resuscitation. Resuscitation begins before delivery with team assembly, equipment check, and briefing. Initial questions follow the GRASP mnemonic (Table 19.1). After delivery, gestational age, muscle tone, and breathing should be recorded for the initial assessment. If the infant is full-term with good tone and normal respirations, the infant should stay with the mother and routine resuscitation should be provided. If these three criteria are not met, routine resuscitation is provided in addition to further assessment. Additional respiratory support can be provided to infants who have breathing difficulty or cyanosis via oxygen or pressure, but an infant who remains apneic or bradycardic requires support with positive pressure ventilation. Monitoring oxygen saturation and heart rate with pulse oximetry (SpO_2) and ECG, respectively, should also be considered at this point. The target preductal (right upper extremity) SpO_2 values at each time point should be the range between the numbers above and below the time point in the inset. Positive pressure ventilation (PPV) should continue for an infant who remains bradycardic or apneic. The effectiveness of ventilation should be assessed, and ventilation corrective steps (mnemonic—MRSOPA) should be performed as needed. Finally, if the heart rate (HR) decreases to <60 beats per minute (bpm) and does not improve with adequate ventilation, then tracheal intubation, chest compressions, and 100% oxygen should be provided. At this time, further therapy with medications and assessment for additional confounding issues such as pneumothoraces or hypovolemia (correcting with normal saline—NS) should be considered. (Modified from Maheshwari Evidence Based Neonatology and Textbook of Neonatal Resuscitation [2], Copyright Satyan Lakshminrusimha)

Table 19.1 ETT size for babies based on estimated gestational age (GA—weeks) or birth weight (kg)

GA (weeks)	Weight (kg)	ETT size	Suction catheter size	Laryngoscope blade
>34	>2	3.5	8 F	No. 1
28–34	1–2	3.0	6 F or 8 F	No. 0
<28	<1	2.5	5 F or 6 F	No. 0 or 00

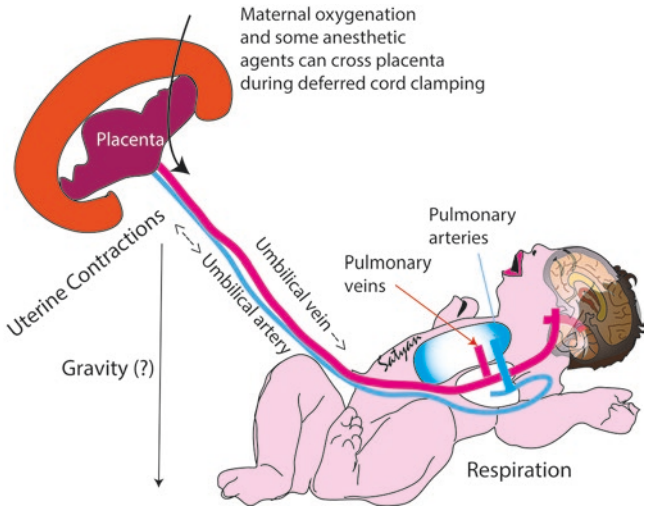


Fig. 19.6 Factors that influence a placental transfusion. Modified from [6] to indicate the importance of uterine contractions, gravity (although this plays a small role in the presence of vigorous uterine contractions), and presence of spontaneous respirations (crying). (Copyright Satyan Lakshminrusimha)

Positioning

The majority of neonates only require routine care and can be held by the mother. Non-vigorous infants and preterm neonates without good tone and with poor respiratory effort, apnea, or grunting need to be placed under a radiant warmer. These infants initially need positioning, stimulation, and warmth. The baby should be positioned supine with the head and neck slightly extended in the "sniffing position." A shoulder role may be useful for infants with a large occiput from molding. If secretions are obstructing the airway, the mouth should be cleared first followed by the nares by gentle suction.

Temperature Management

Wet skin increases evaporative fluid loss (Fig. 8.6, Chap. 8). Removing fluid from the skin by drying with a warm, dry blanket is the first step in reducing heat loss. If more drying is required, discard the wet towel and use a new dry towel (Fig. 19.7). In preterm infants, placing them immediately in a polyethylene plastic before drying is also effective in reducing heat loss by evaporation. A combination of interventions such as increasing the environmental temperature to 24–26 °C (75–80 °F) and using warm blankets, a plastic covering without drying, and a thermal mattress (Fig. 19.7) is effective in preventing hypothermia. It is important to avoid hyperthermia in asphyxiated infants as it may predispose to poor outcomes [8].

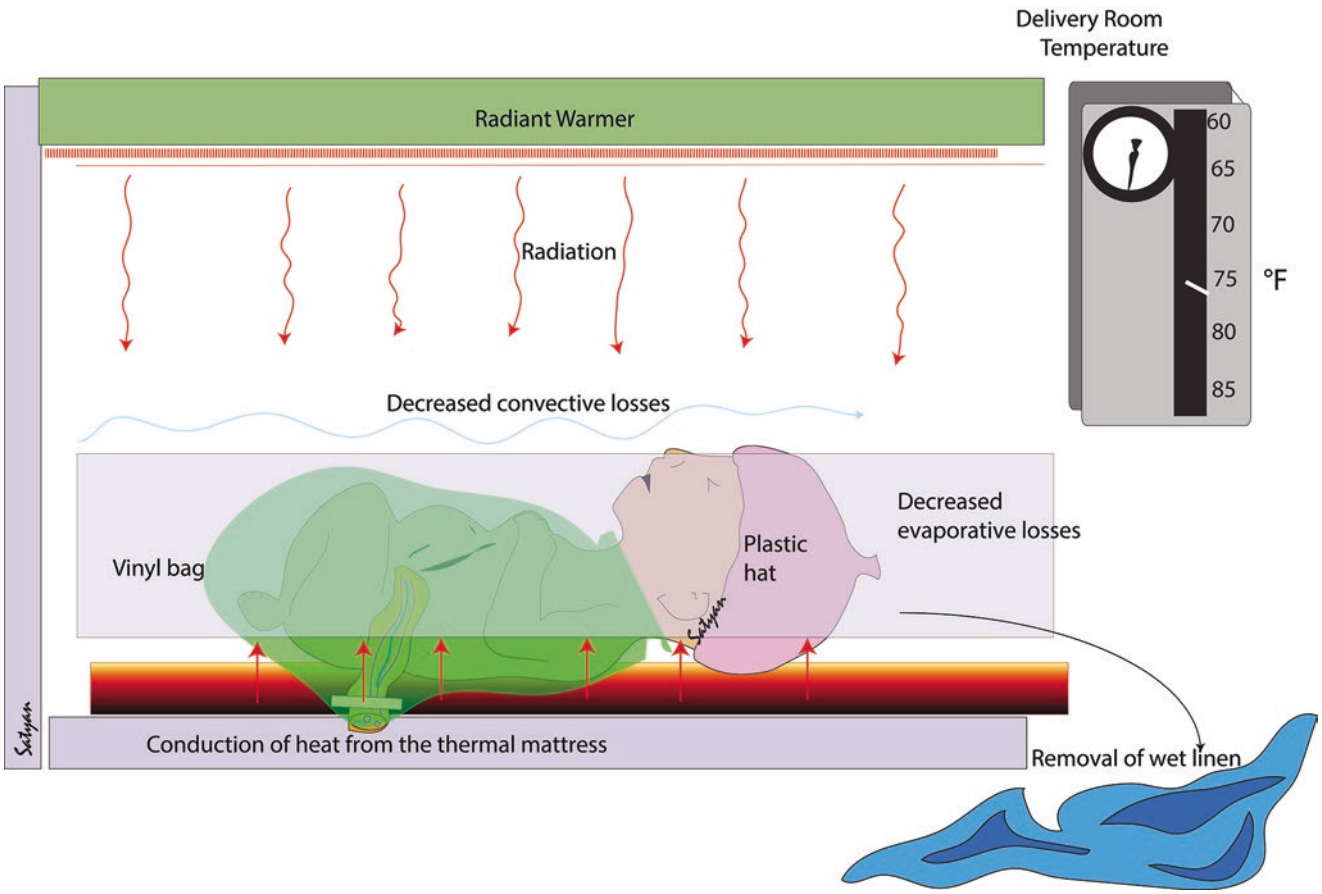


Fig. 19.7 Mechanisms of heat loss during resuscitation. The neonate has the potential to gain or lose heat by four mechanisms: radiation, conduction, convection, and evaporation (See Chap. 8, Fig. 8.6). Heat is lost to surrounding surfaces that are not in direct contact with the infant via radiation and is proportional to the temperature difference between the infant's body and the environmental sources. A radiant warmer provides a source of radiant heat to counteract heat losses. Increasing the temperature of the DR can also decrease the amount of heat loss by radiation and convection. Conduction is the route by which neonates gain or lose the least amount of heat. Conduction heat energy is transferred between surfaces that are in direct contact. An infant can lose heat via conduction if placed on a cooler surface and gain heat if in contact with a warmer surface such as a heated mattress. Heat can also be transferred via convection by air passing over the infant. The temperature in the DR is cooler than the infant, so the infant loses heat by this mechanism. This source of heat loss can be minimized by increasing the DR temperature and ensuring the sides of the radiant warmer are up and surrounding the infant to minimize convection heat loss. Finally, the infant can lose heat by evaporation. This can be reduced by drying the neonate immediately after delivery or with the use of a polyurethane hat placed on the head and polyurethane bag or wrap covering the infant's body in premature infants. Modified from Mathew et al. [55] (Copyright Satyan Lakshminrusimha)

Stimulation

In addition to stimulation by positioning, clearing secretions if needed, and drying, gently rubbing the back, trunk, or extremities will assist in initiating and supporting spontaneous breathing. If a neonate remains apneic despite stimulation for a few seconds, PPV should be initiated without delay.

Monitoring

In infants that require resuscitation beyond stimulation, assessment of oxygenation, respiration, and heart rate is important. Assessment of color is not accurate, whereas placement of a pulse oximeter on the right upper extremity to monitor preductal SpO_2 is vitally important (Fig. 19.8).

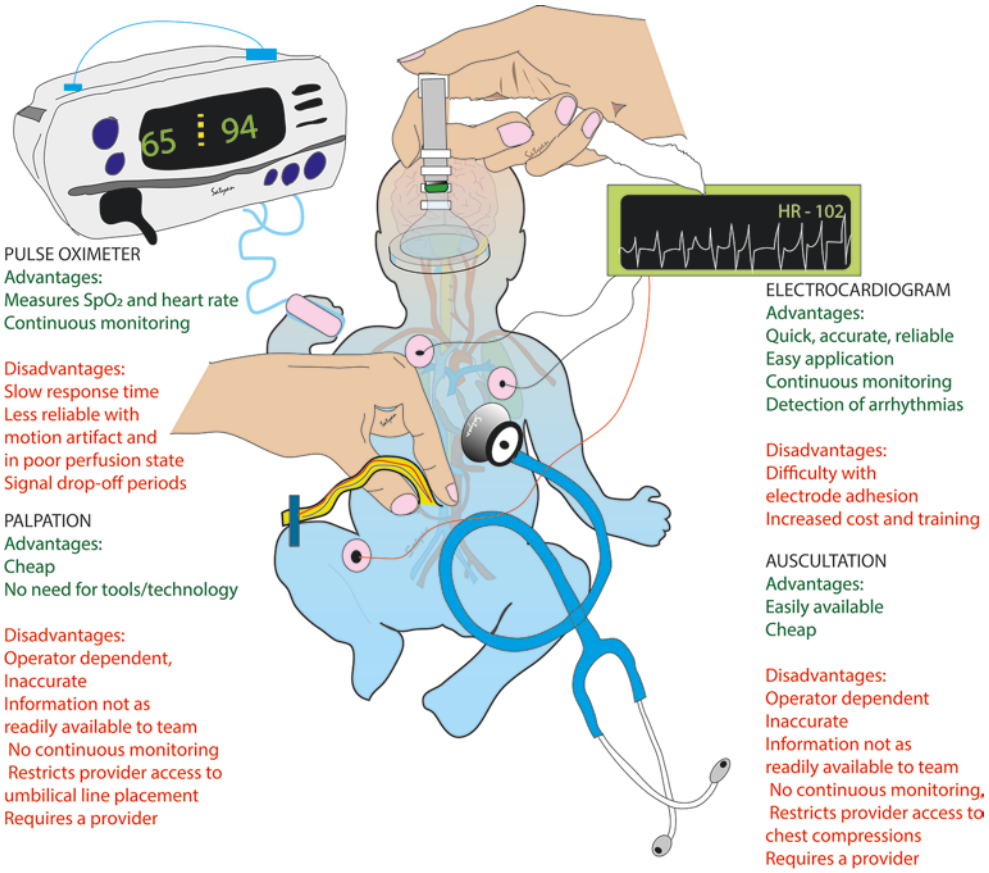


Fig. 19.8 Methods to assess the heart rate in the DR. There are four methods to assess heart rate in the DR, each with advantages and disadvantages. The method chosen should be based on the availability of equipment and training of providers. Electrocardiography is the most accurate method and is most widely recommended for use in the DR, but this resource is not always available. Pulse oximetry is more reliable than other methods, but there may be a lag time before an accurate heart rate is displayed and requires adequate perfusion. Pulse oximeter monitors are not immediately available in every DR. Both umbilical cord palpation and auscultation with a stethoscope are not as accurate as pulse oximetry or electrocardiography and do not provide continuous monitoring. However, these approaches use equipment that is readily available in most DRs. Modified from Vali et al. [9] (Copyright Satyan Lakshminrusimha)

Heart rate can be monitored by pulse oximetry, palpation of pulsations of major arteries (including the umbilical stump), auscultation, EKG, and Doppler/echocardiographic measurements (Fig. 19.8). Placement of EKG leads is a quick, reliable method to measure the heart rate in the DR [9].

Approach to an Infant Born Through Meconium Stained Amniotic Fluid (MSAF—Fig. 19.9)

In the 1990s, amnioinfusion, suctioning at the perineum, and tracheal suctioning for both vigorous and non-vigorous infants were steps in the management of an infant born through MSAF (Fig. 19.9). With evidence from three large randomized controlled trials [10–12] involving close to 2000 mother-infant dyads in each trial, tracheal suctioning for vigorous infants, suctioning before the delivery of shoulders, and amnioinfusion all failed to impact the incidence of meconium aspiration syndrome (MAS) [13]. Before 2015, non-vigorous infants born through MSAF underwent routine tracheal suction [13]. Based on the results from four small randomized controlled trials from India [14–17] that showed no difference in mortality or the incidence of MAS among non-vigorous infants with tracheal suctioning, NRP now recommends initiation of PPV without routine immediate direct laryngoscopy with tracheal suctioning in non-vigorous neonates delivered through MSAF [1]. MSAF remains a significant risk factor for needing advanced resuscitation. If meconium obstructs the airway and prevents chest rise with PPV, suctioning may be needed [1].

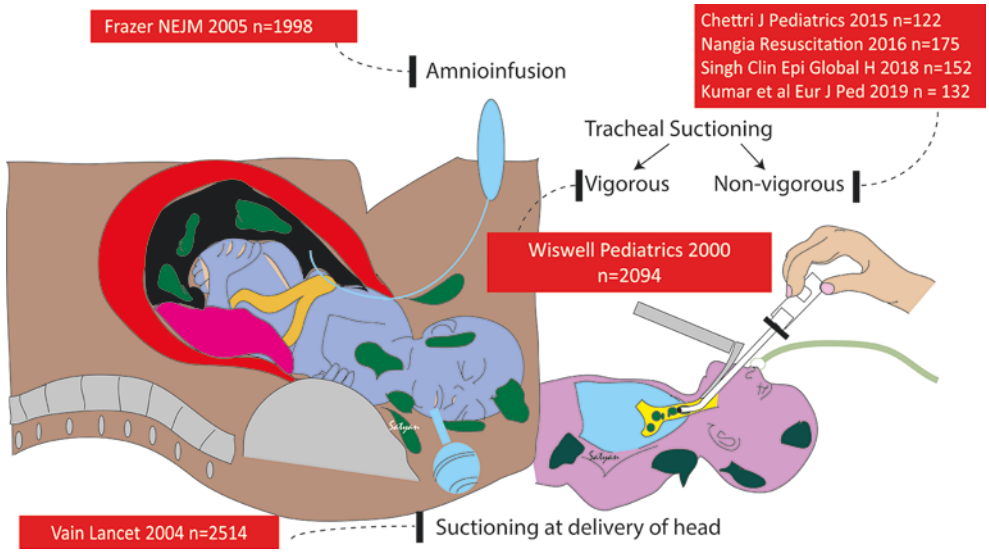
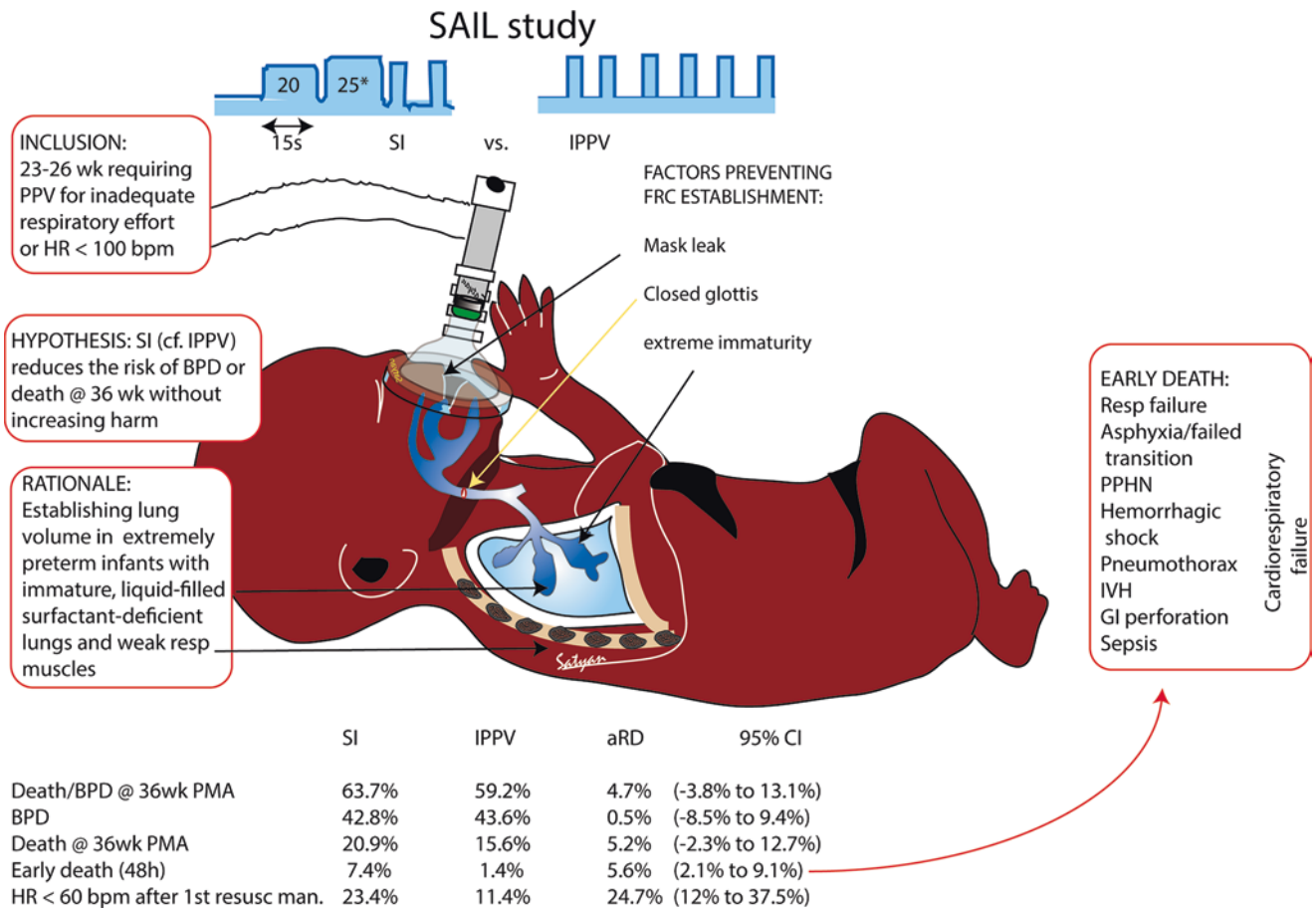


Fig. 19.9 Management of infants born through meconium stained amniotic fluid (MSAF) in the 1990s. Randomized controlled trials (*n* = number of mother-infant dyads enrolled in these trials) evaluating various indications for these interventions are shown. See text for details. Modified from Rawat et al. [13]—Copyright Satyan Lakshminrusimha

Positive Pressure Ventilation (PPV)

Most neonates breathe spontaneously after birth within 30–60 s with stimulation. PPV is indicated if neonates do not breathe within the first 60 s with stimulation or are persistently bradycardic with heart rate < 100 beats per min (bpm). Compared with older children and adults, neonates enter into secondary apnea before the onset of cardiac arrest (Fig. 19.4). Hence, respiratory support should precede chest compressions during neonatal resuscitation [18]. Initial breaths with a peak inflation pressure (PIP) of 20–25 cm H_2O and positive end-expiratory pressure (PEEP) of 5 cm H_2O are provided at a rate of 40–60/min. The inflation time should be kept brief at ≤1 s. Sustained inflation greater than 10 s can be harmful in preterm infants and should be avoided based on the results from the SAIL study (Fig. 19.10) [19]. In spontaneously breathing infants who require respiratory support, but who have heart rates >100 bpm, continuous positive airway pressure (CPAP) should be provided.

Mask ventilation is ineffective in some infants due to a poorly fitting facemask, inappropriate position of the head, obstruction by secretions, or inadequate PIP. Corrective measures using the mnemonic MRSOPA focus on effective ventilation of the lung (Fig. 19.9). If mask ventilation fails to cause the chest to rise, alternative airways such as a laryngeal mask or tracheal tube should be used. (Fig. 19.11).



	SI	IPPV	aRD	95% CI
Death/BPD @ 36wk PMA	63.7%	59.2%	4.7%	(-3.8% to 13.1%)
BPD	42.8%	43.6%	0.5%	(-8.5% to 9.4%)
Death @ 36wk PMA	20.9%	15.6%	5.2%	(-2.3% to 12.7%)
Early death (48h)	7.4%	1.4%	5.6%	(2.1% to 9.1%)
HR < 60 bpm after 1st resusc man.	23.4%	11.4%	24.7%	(12% to 37.5%)

Fig. 19.10 A graphic abstract outlining the SAIL study that evaluated sustained inflation vs. PPV during initial resuscitation [19]. Inclusion criteria, hypothesis, rationale, and results are shown. Early death (during the first 48 h after birth) occurred more frequently in premature neonates who were randomized to receive sustained inflations. Causes of early death are listed in the inset. *BPD* bronchopulmonary dysplasia, *bpm* beats per minute, *GI* gastrointestinal, *HR* heart rate, *IPPV* intermittent positive pressure ventilation, *IVH* intraventricular hemorrhage, *PPHN* persistent pulmonary hypertension of the neonate, *SI* sustained inflation. Copyright Satyan Lakshminrusimha

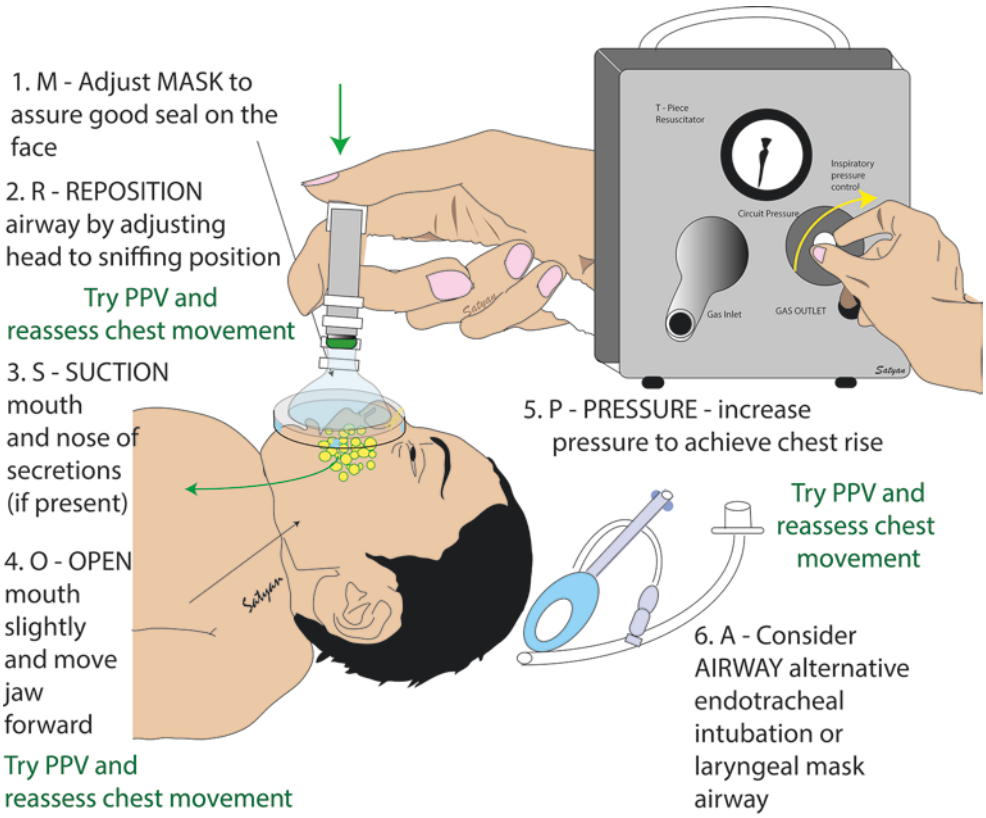


Fig. 19.11 Corrective steps to improve efficacy of ventilation. These steps use the mnemonic MRSOPA. After these corrective measures, PPV should be attempted as shown and chest rise evaluated. (Copyright Satyan Lakshminrusimha)

Oxygen

In term infants ≥35 weeks gestation, resuscitation is initiated with 21% oxygen and titrated up based on preductal SpO_2 in the right upper limb [18, 20]. In preterm infants 28–34 weeks gestation, most guidelines recommend the use of 21 to 30% oxygen (Fig. 19.12). The optimal initial oxygen for resuscitation of preterm infants <28 weeks is controversial. The NRP recommends 21–30% [18] but several experts prefer to use ~30% oxygen. In extremely preterm infants who require mask ventilation, the oxygen gradient from inspired oxygen to alveolar gas and from alveolar gas to arterial gas (A-a gradient) might be large in extremely preterm infants due to their lungs being immature in the canalicular stage. In all neonates, it is not recommended to begin resuscitation with 100% oxygen because of its association with a greater mortality in term infants [18]. A meta-analysis of studies that compared low (≤ 30% oxygen) vs. high (≥ 60%) inspired oxygen for initial resuscitation of infants failed to demonstrate significant differences in outcome [21]. A summary of current findings is shown in Fig. 19.13.

When depressed infants require chest compressions (see below), the inspired oxygen should be set to 100% due to compromised pulmonary, coronary, and cerebral blood flow [22].

Frequent assessment of oxygenation using the pulse oximetry chart in Fig. 19.12 and titration of inspired oxygen is important [23]. The main goal is to achieve a heart rate of >100 bpm within 2 min and a preductal SpO_2 of 80–85% by 5 min. Failure to achieve these outcomes may increase morbidity and mortality in preterm infants [24, 25].

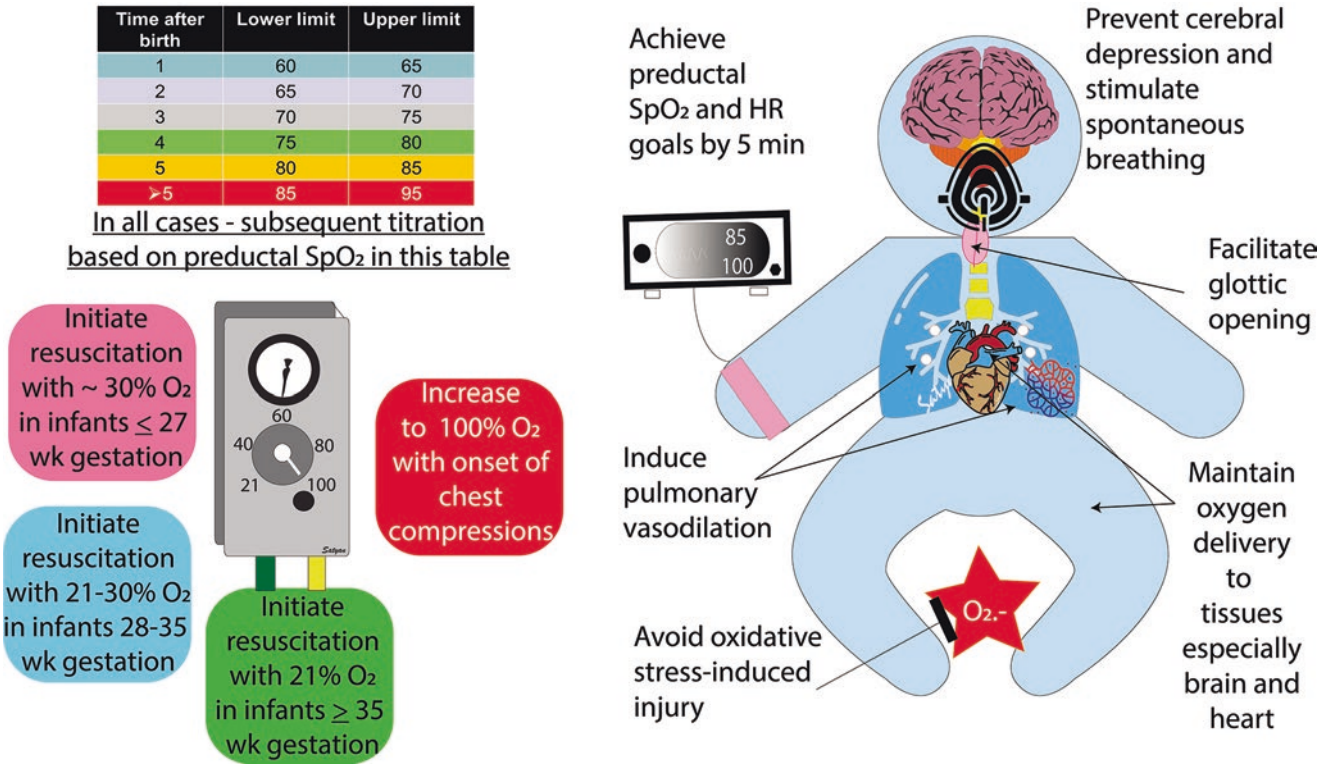


Fig. 19.12 Guidelines for initial titration of oxygen based on references [20] and modified from AHA NRP guidelines [18]. In all cases, preductal SpO_2 should be monitored, and inspired oxygen should be adjusted based on targets shown in the table. However, if chest compressions are needed, inspired oxygen should be immediately increased to 100%. Goals of adjusting inspired oxygen during resuscitation are shown on the right panel. HR: heart rate. Modified from Saugstad et al. [20]. Copyright Satyan Lakshminrusimha

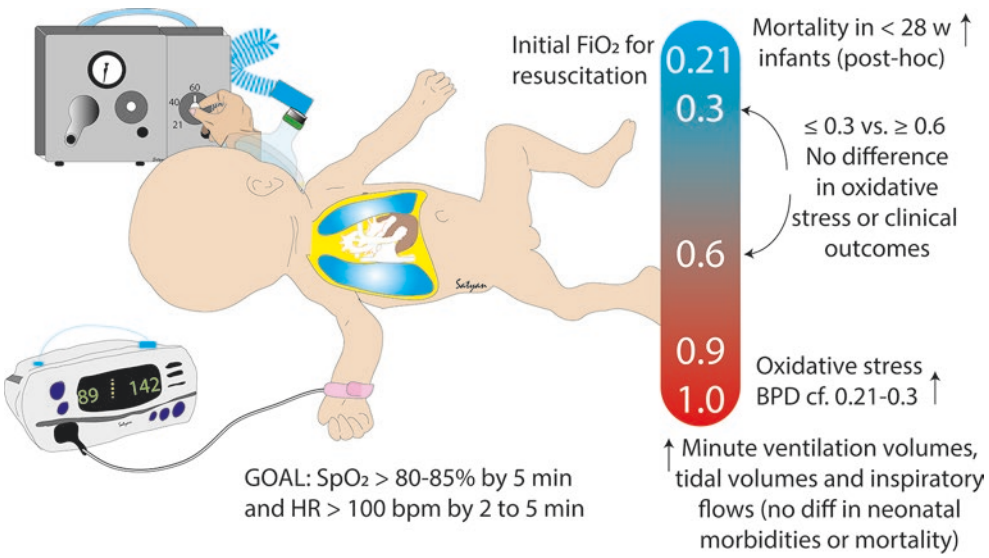


Fig. 19.13 Current evidence on the initial oxygen concentration for resuscitation of extremely preterm infants. The goal of this intervention is to achieve a preductal SpO_2 of ≥80–85% and heart rate (HR) of ≥100 beats per minute (bpm) by 5 min of birth. Systematic reviews and meta-analyses of studies using low initial $FiO_2 \leq 0.3$ vs. high $FiO_2 \geq 0.6$ showed no difference in either clinically meaningful outcomes [21] or oxidative stress markers. One trial in a post hoc analysis showed increased mortality with 0.21 FiO_2 in extremely preterm infants [56], while another trial showed better minute ventilation volumes with an FiO_2 of 1.0 [57]. Copyright Satyan Lakshminrusimha

Intubation

Tracheal intubation is probably the most common procedure for which the neonatal team is likely to seek help from the anesthesiologist. Intubation is often conducted using an uncuffed tube. Typically, uncuffed 2.5, 3.0, 3.5, and 4.0 mm tubes are stocked in the DR. These tubes can be inserted by digital (using a finger), direct laryngoscopy or using a video laryngoscope [26]. A laryngeal mask may serve as an alternative to ineffective bag mask ventilation (for neonates >2000 gm or 34 weeks gestation) or for any neonate whose airway cannot be intubated during resuscitation [27, 28].

Indications for Tracheal Intubation in the DR

(i) Improve ventilation efficacy when mask ventilation is ineffective or inadequate.
(ii) Prolonged PPV—ETT improves the efficacy and ease of ventilation.
(iii) During chest compressions—To maximize efficacy.
(iv) Diaphragmatic hernia—To minimize air entering the stomach.
(v) Surfactant administration.
(vi) Removal of obstruction by direct suction.

Size of the ETT

Size of the ETT is based on estimated gestational age or weight (Table 19.1).

Confirmation of Tube Position

The two primary methods used to confirm correct placement of the ETT are a rapidly increasing heart rate and SpO_2 and detection of exhaled CO_2. Other indicators included (a) audible and equal breath sounds over both axillae during PPV, symmetrical chest rise, absent air entry over the stomach, little or no air leak from the mouth during PPV, and mist in the ETT (Fig. 19.14).

In some situations where ventilation and/or perfusion of the lungs is inadequate, the CO_2 detector may not show a color change even though the ETT is in the trachea. Possible conditions where such false negative CO_2 detector color change might occur are shown in Fig. 19.15. Occasionally, the CO_2 detector may change color to yellow even though the ETT is not in the trachea. This occurs when the CO_2 detector has been contaminated with epinephrine (and possibly gastric acid—although uncommon), if vigorous mask ventilation has pushed exhaled breath into the stomach, or if the CO_2 detector is defective and has changed color in the package before use [2].

Depth of Insertion of ETT in Neonates (Fig. 19.16)

The trachea is very short in neonates (especially in extremely preterm infants), 4–4.5 cm. It is important to place the tip of the ETT below the vocal cords but above the carina to avoid a right mainstem intubation. Because the right upper lobe bronchus may take off from the trachea (in up to 2% of patients) more commonly in Down syndrome, VACTERL, and others, it is important that the tube is midtracheal. Gestational age is a reasonable predictor of the correct insertion depth for orotracheal intubation. A table based on Kempley et al. is shown in Fig. 19.16 [29]. The nasal septum-tragus length (NTL) [30], oro-helical length [31], and sternal length have also been used to calculate the "tip-lip" depth of an orotracheal tube. The NTL (sometimes adjusted by adding 0.5–1 cm) is most commonly used. The Tochen formula, also known as the 7-8-9 rule, was crafted to predict the "tip to lip" length of the tracheal tube based on the neonate's weight (6 cm + 1 cm/kg body weight) [32]. The formula is easy to remember and accurate in full size neonates but more likely to predict the tip of the tube too deep in low birth weight and extremely premature infants. Hence, the 'modified' Tochen formula (5 cm + 1 cm/kg body weight), which reduced the depth of the tube by 1 cm, positioned the tip of the tube more frequently mid-tracheal in low birthweight and extremely premature infants was introduced [33]. A recent systematic review of all formulae that predict the optimal depth of the orotracheal tube [34] and a randomized controlled trial that compared three formulae—the Tochen, Kempley, and NTL—both concluded that "tip to lip" formulae equally predicted malpositioned tracheal tubes in neonates [35]. We recommend that a chest X-ray should be reviewed to verify the position of the tip of the tracheal tube in all neonates notwithstanding the formulae used, to minimize the risk of complications and optimize the delivery of medications via the tracheal tube.

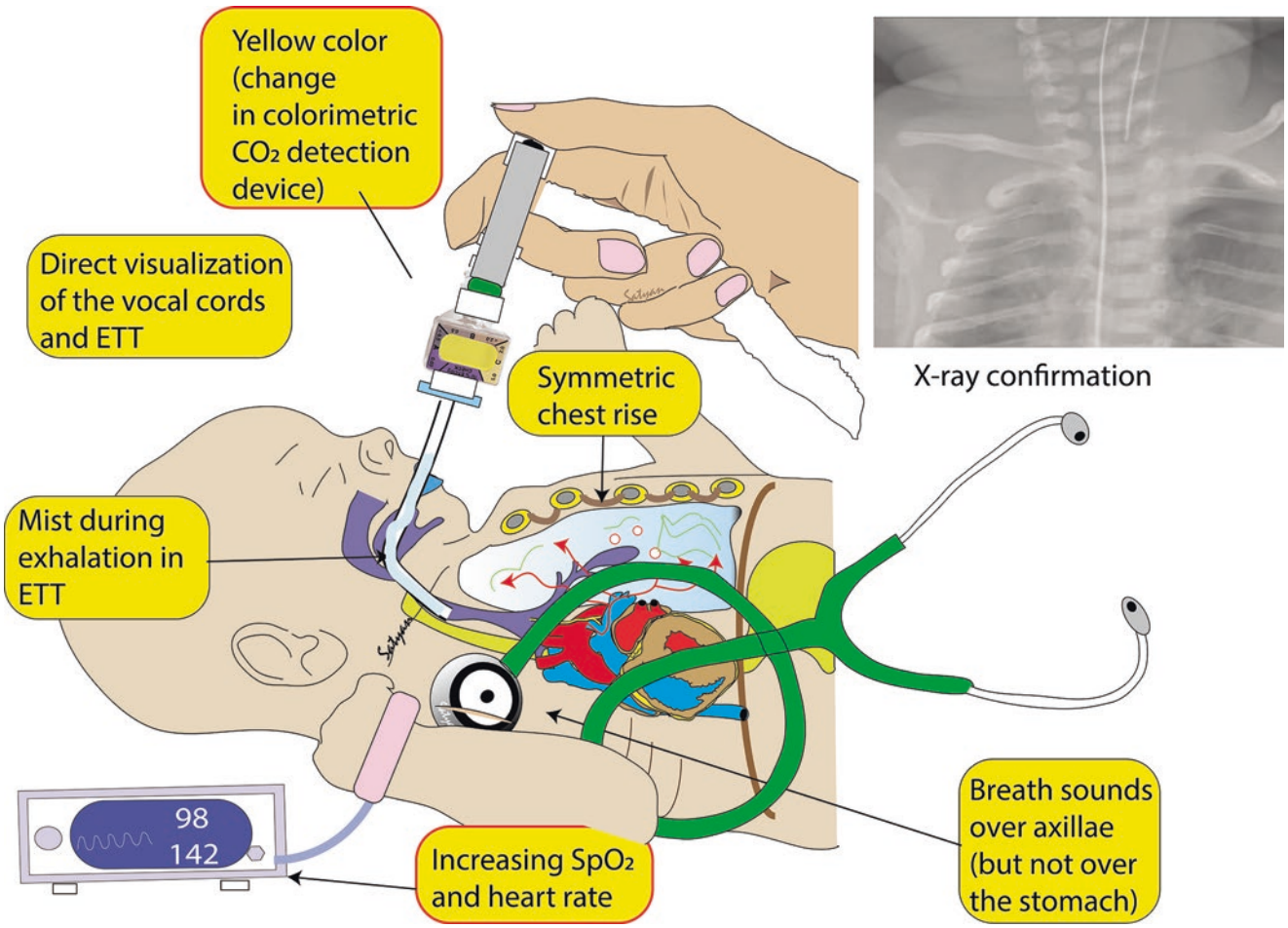


Fig. 19.14 Methods to confirm the position of the ETT within the trachea. The primary methods are shown in red squares. Copyright Satyan Lakshminrusimha

Deterioration after Intubation

Sudden deterioration after intubation can be due to displacement of the ETT (too far into the right main stem or pulled back into pharynx or moved into the esophagus), obstruction by mucus plug or blood or meconium, development of a pneumothorax, or other air-leak syndrome or equipment failure (disconnections in the ventilator circuit or loss of pressure in the gas source). The mnemonic DOPE outlines these conditions [2].

- Displaced ETT.
- Obstructed ETT.
- Pneumothorax.
- Equipment failure.

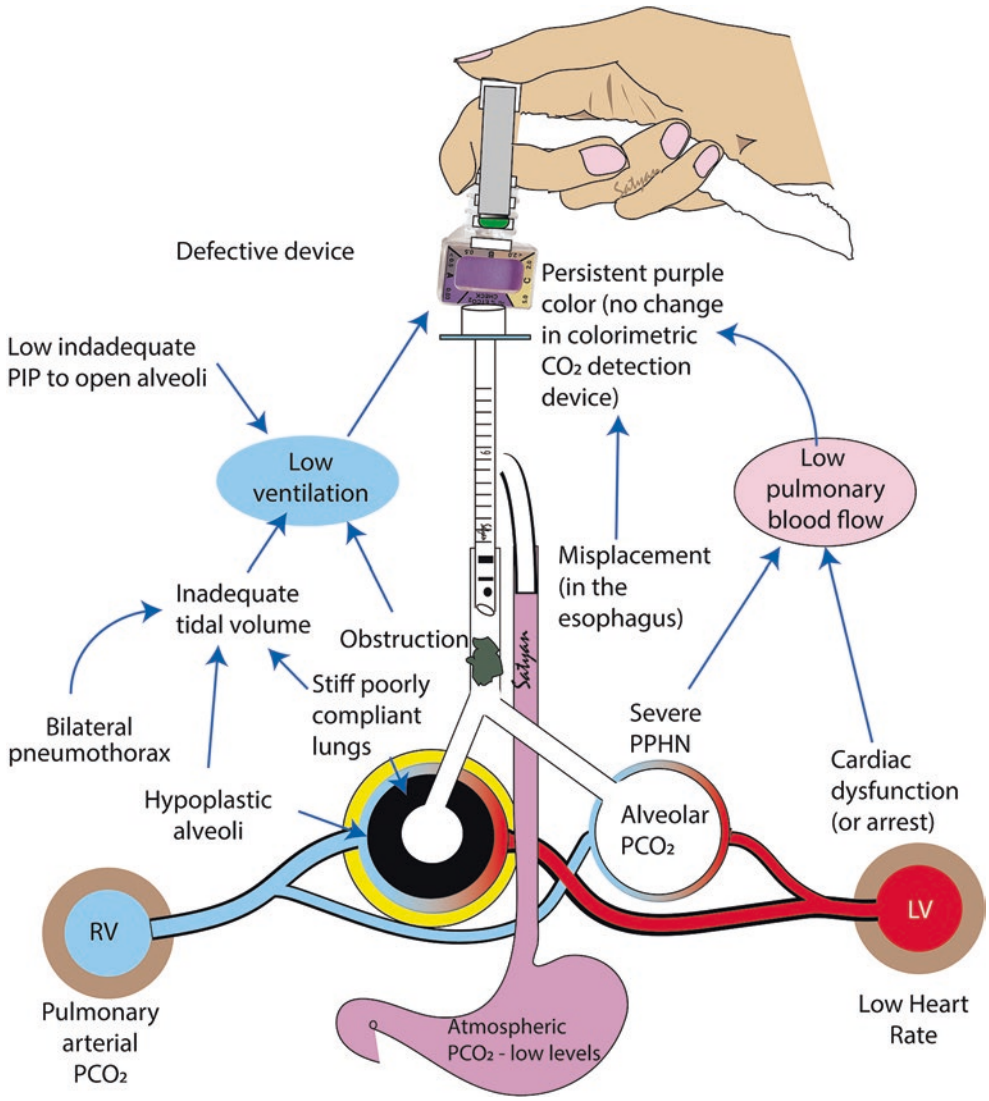
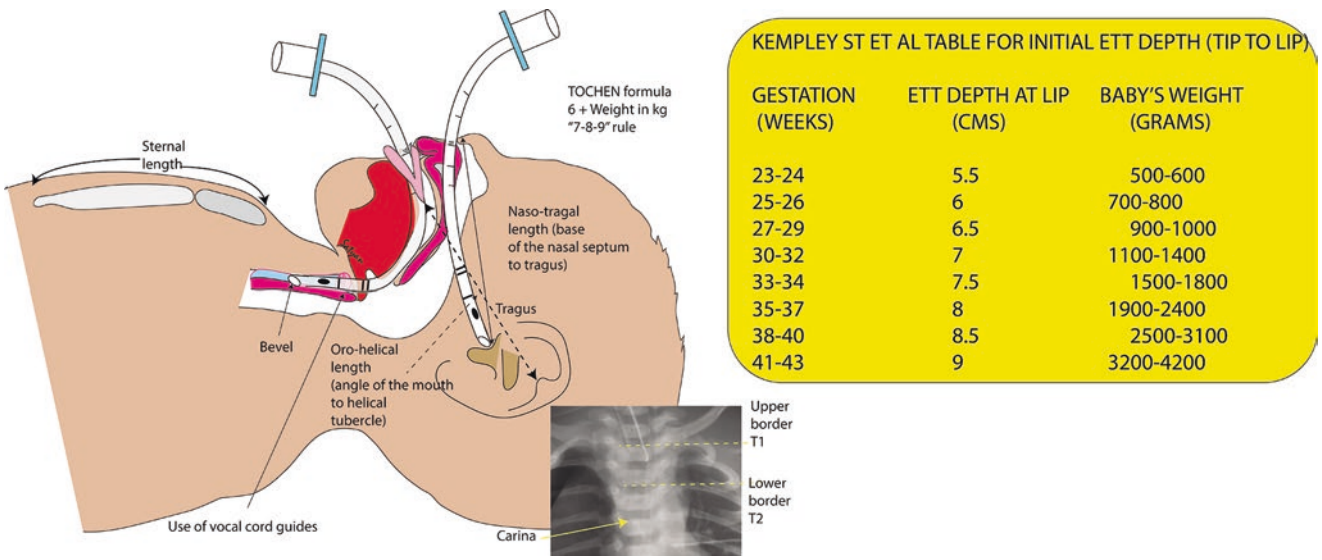


Fig. 19.15 Causes for persistent purple coloration of colorimetric CO_2 detector in neonates. The most common reason is esophageal intubation. The other causes can be classified into inadequate ventilation and poor perfusion. Extreme prematurity can be associated with both hypoventilation and low pulmonary flow. LV: left ventricle; PIP: positive inspiratory pressure; RV: right ventricle. Copyright Satyan Lakshminrusimha



KEMPLEY ST ET AL TABLE FOR INITIAL ETT DEPTH (TIP TO LIP)

GESTATION (WEEKS)	ETT DEPTH AT LIP (CMS)	BABY'S WEIGHT (GRAMS)
23-24	5.5	500-600
25-26	6	700-800
27-29	6.5	900-1000
30-32	7	1100-1400
33-34	7.5	1500-1800
35-37	8	1900-2400
38-40	8.5	2500-3100
41-43	9	3200-4200

Fig. 19.16 Formulas, measurements, and table to predict the depth of ETT insertion in neonates. See text for details. Copyright Satyan Lakshminrusimha

Chest Compressions

The etiology of cardiac arrest in newly born infants differs from that of adults. Neonatal cardiac arrest in the DR arises from profound bradycardia as a result of oxygen depletion, carbon dioxide accumulation, and increasing lactic acidosis secondary to asphyxia. Therefore, ventilation remains critical in establishing return of spontaneous circulation (ROSC), and resuscitation with exclusive chest compressions in asphyxiated piglet models is ineffective [36, 37]. Chest compressions are indicated for those neonates whose heart rate (HR) remains <60 bpm in the presence of adequate ventilation.

Severe asphyxia can lead to substrate depletion and profound vasodilation, which can influence the effect of chest compressions on hemodynamic parameters. The primary determinant in successful cardiopulmonary resuscitation (CPR) depends on adequate myocardial blood flow. Measuring myocardial blood flow is not currently practical. Therefore, coronary perfusion pressure (CPP), the difference between the right atrial diastolic pressure and the diastolic aortic pressure, serves as a surrogate for myocardial flow (Fig. 19.17). Animal studies have demonstrated that a greater CPP (>20 mm Hg) improves the likelihood of achieving ROSC and, therefore, better survival rates [38–40]. In the clinical setting, patients who had a greater CPP (>25 mm Hg) during CPR had a greater likelihood of ROSC [41]. However, prospective clinical trials have not confirmed that targeting CPP during CPR improves survival. Furthermore, the impact of CPP in predicting ROSC in neonates is unknown. Experiments on adult pigs with ventricular fibrillation-induced cardiac arrest have shown a stepwise increase in diastolic blood pressure with each successive chest compression and an abrupt decrease in blood pressure after interruption of chest compressions [42]. In the presence of a ductus arteriosus, it is not clear if this relationship is maintained in neonates during chest compressions in the DR (Fig. 19.17). In newly born lamb models, coronary perfusion occurs during diastole during intrinsic beats and decompression phase during CPR, whereas cerebral perfusion occurs during systole during intrinsic beats and compression phase during CPR (Fig. 19.17a–c).

The current recommended compression-to-ventilation (C:V) ratio for neonatal resuscitation of 3:1 is based on expert opinion and was made in an attempt to match the respiratory and heart rate in the neonate. Interestingly, this ratio provides 30 breaths and 90 compressions in 1 min, which are significantly less than the intrinsic respiratory rate of 40 breaths and heart rate of 120–160 beats per minute in the neonate. The optimal ventilation strategy immediately after birth has not been determined, and different C:V ratios have not improved outcomes in preclinical and neonatal manikin models [43–47]. A recent study in a perinatal asphyxiated lamb model with fluid-filled lungs and a transitioning circulation, mimicking the neonate in the DR, in which continuous uninterrupted chest compressions (at a rate of 120) were compared with asynchronous ventilation to 3:1 C:V has shown greater oxygen delivery to the brain, but no difference in the incidence or time to ROSC [48].

It is important to summon additional personnel if the newly born infant requires chest compressions. The inspired oxygen should be increased to 100% [22]. If the HR after birth remains <60 bpm despite adequate PPV for at least 30 s, it is reasonable to initiate chest compressions (Fig. 19.18).

Several factors other than the chest compression rate impact CPR success including i) the depth of compressions, ii) full recoil between compressions, and iii) the method of chest compressions and provider performance (Fig. 19.19). The depth of chest compressions should be approximately one-third of the anterior-posterior chest diameter and be sufficient to generate a palpable pulse. In neonates, the two-thumb technique is the preferred method to provide chest compressions. The thumbs are placed together (side by side or one on top of the other) on the lower third of the sternum, while the hands encircle the chest and fingers support the back. This technique delivers greater blood pressures, superior depth, and less variability with each chest compression when compared with the two-finger method (the tips of the middle and either ring or index finger placed over the sternum) [49].

Poor response to chest compressions and PPV should alert the resuscitator to check the efficacy of various interventions and the presence of other factors such as pneumothorax, pneumopericardium, and blood loss. This checklist goes with the mnemonic CARDIO and is shown in Table 19.2 [2]. If HR remains <60 bpm, epinephrine should be prepared to be administered through either the ETT or an umbilical venous catheter (see next section).

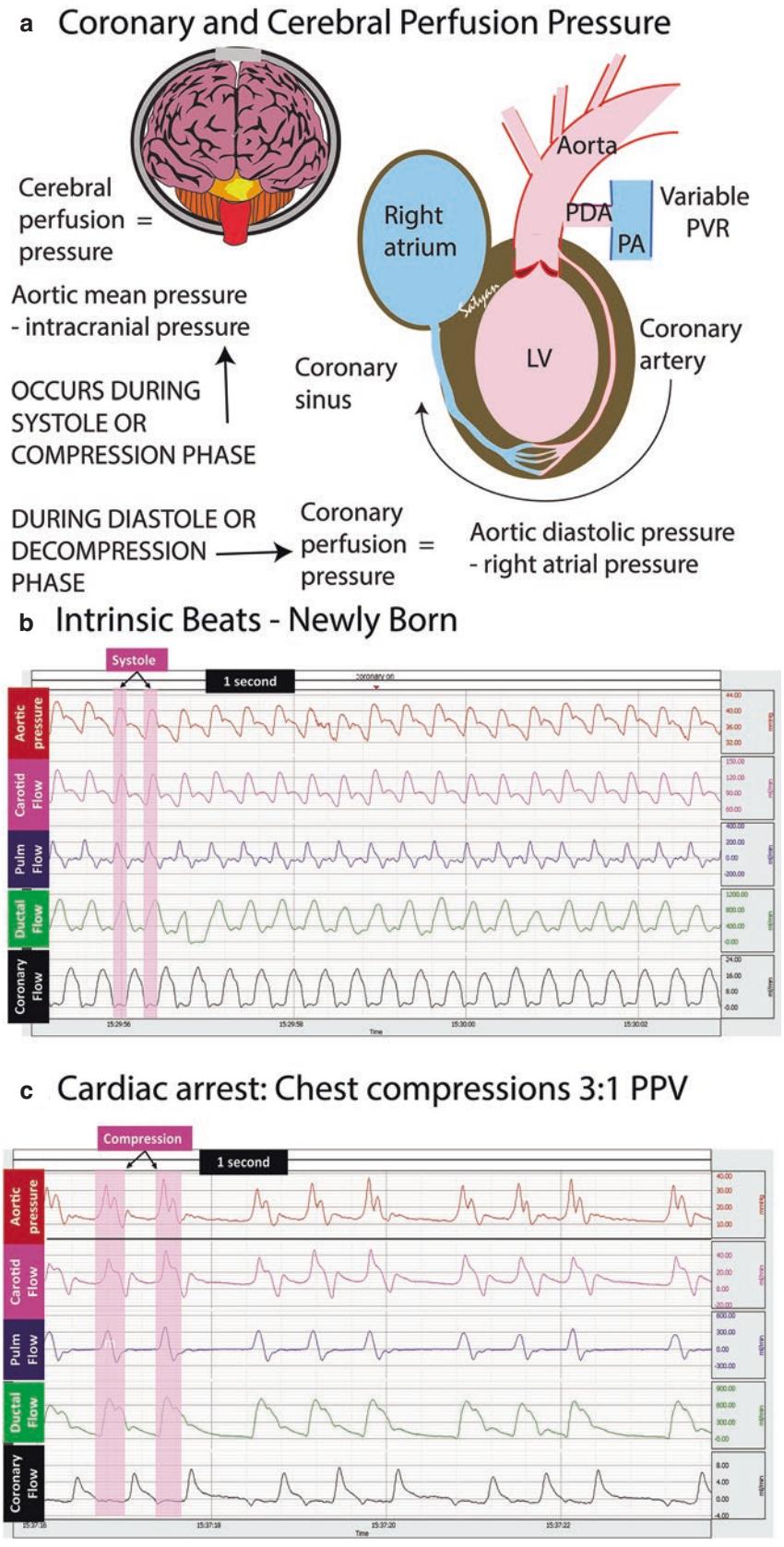


Fig. 19.17 Determinants of cerebral and coronary blood flow (**a**) during intrinsic heart beats (**b**) and chest compressions (**c**) at 3:1 ratio with positive pressure ventilation (PPV). In the presence of a large patent ductus arteriosus (PDA) and variable pulmonary vascular resistance (PVR) soon after birth, achieving physiological diastolic pressure during chest compressions is difficult during cardiac arrest (**c**). Carotid flow occurs during the systolic or compression phase, and coronary flow occurs during diastolic or decompression/relaxation phase. Copyright Satyan Lakshminrusimha

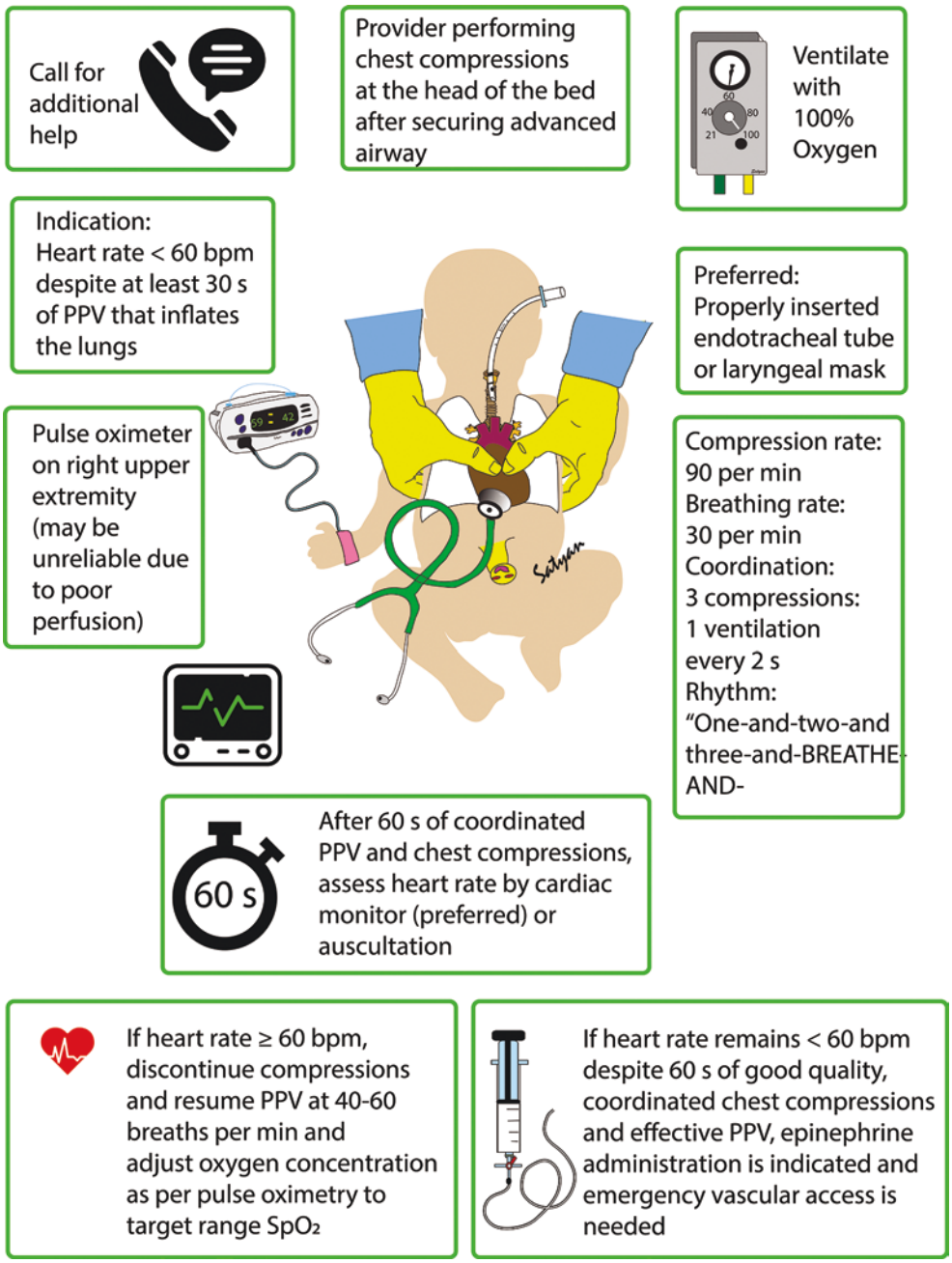


Fig. 19.18 Preparation, indications, and procedure for chest compressions. Copyright Satyan Lakshminrusimha

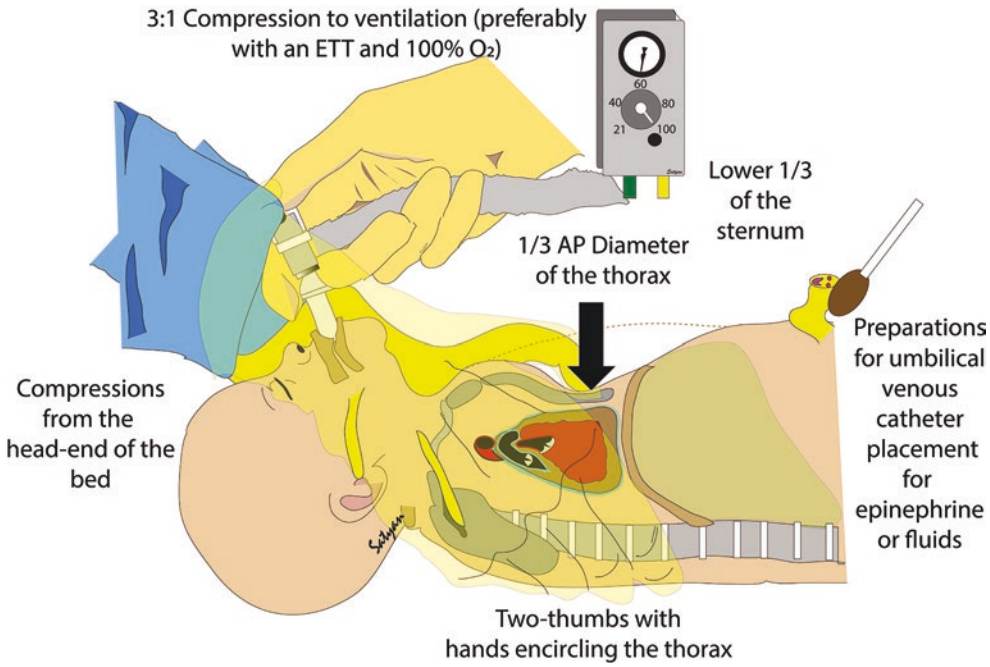


Fig. 19.19 Procedure for providing chest compressions. Effective ventilation can be provided with an endotracheal tube (ETT) and 100% inspired oxygen. With thumbs placed on the lower third of the sternum, with fingers encircling the thorax, and compressing one-third anteroposterior (AP) diameter of the thorax, adequate pressures can be generated. Preparation to place an umbilical venous catheter for administration of epinephrine or fluids is the next step if positive pressure ventilation and chest compressions are not effective. Copyright Satyan Lakshminrusimha

Table 19.2 Questions to ask when heart rate is not improving with compressions and ventilation (mnemonic CARDIO)

1. **C**hest movement: Is the chest moving with each breath?
2. **A**uscultation: Are bilateral breath sounds audible?
3. **R**ate: Are three compressions plus one ventilation well-coordinated and being delivered every 2 s?
4. **D**epth: Is the depth of compressions adequate (one-third the AP diameter of the chest)?
5. **I**nspired **o**xygen: Is 100% oxygen being administered through the PPV device?
6. **Other causes:** Air leak, anemia.

Epinephrine in the DR

Epinephrine is the only vasoactive drug recommended by the International Liaison Committee on Resuscitation (ILCOR) for neonates who remain severely bradycardic (HR < 60 bpm) or in cardiac arrest after effective ventilation has been established (Fig. 19.20). The preferred route of administration is intravascular, and access through the umbilical vein by insertion of an umbilical vein catheter may be the best option in the poorly perfused neonate. Epinephrine may be given through the ETT while intravenous (IV) access is attempted. It can also be administered through the intraosseous route (IO) [2].

Epinephrine is available in two concentrations (1 mg/1 mL and 1 mg/10 mL), and selecting the wrong concentration can result in a tenfold dosing error. The recommended tracheal (ET) dose is 0.05–0.1 mg/kg whereas the intravenous dose is 0.01–0.03 mg/kg [1]. Based on animal data, and to simplify the required calculations [50, 51], it would be reasonable to administer 0.1 mg/kg (or 1 mL/kg of 1 mg/10 mL epinephrine) by the ET route in neonates in the DR who have fluid-filled lungs. It may also be more practical to use an IV dose of 0.02 mg/kg (or 0.2 mL/kg of 1 mg/10 mL epinephrine). A dose of 0.02 mg/kg enables use of a 1 mL syringe for a wide range of birth weights from 500 g to 5 kg. At this dose, 0.1 mL of epinephrine can be reliably prepared in a 1 mL syringe for an extremely premature infant weighing 500 g [52].

If the first epinephrine dose is given by the ET route, the IV dose can be administered as soon as intravascular access is established. Repeat doses of epinephrine should be given every 3 min. If IV access cannot be obtained, epinephrine can also be given through an intraosseous device inserted into the proximal tibia in term neonates.

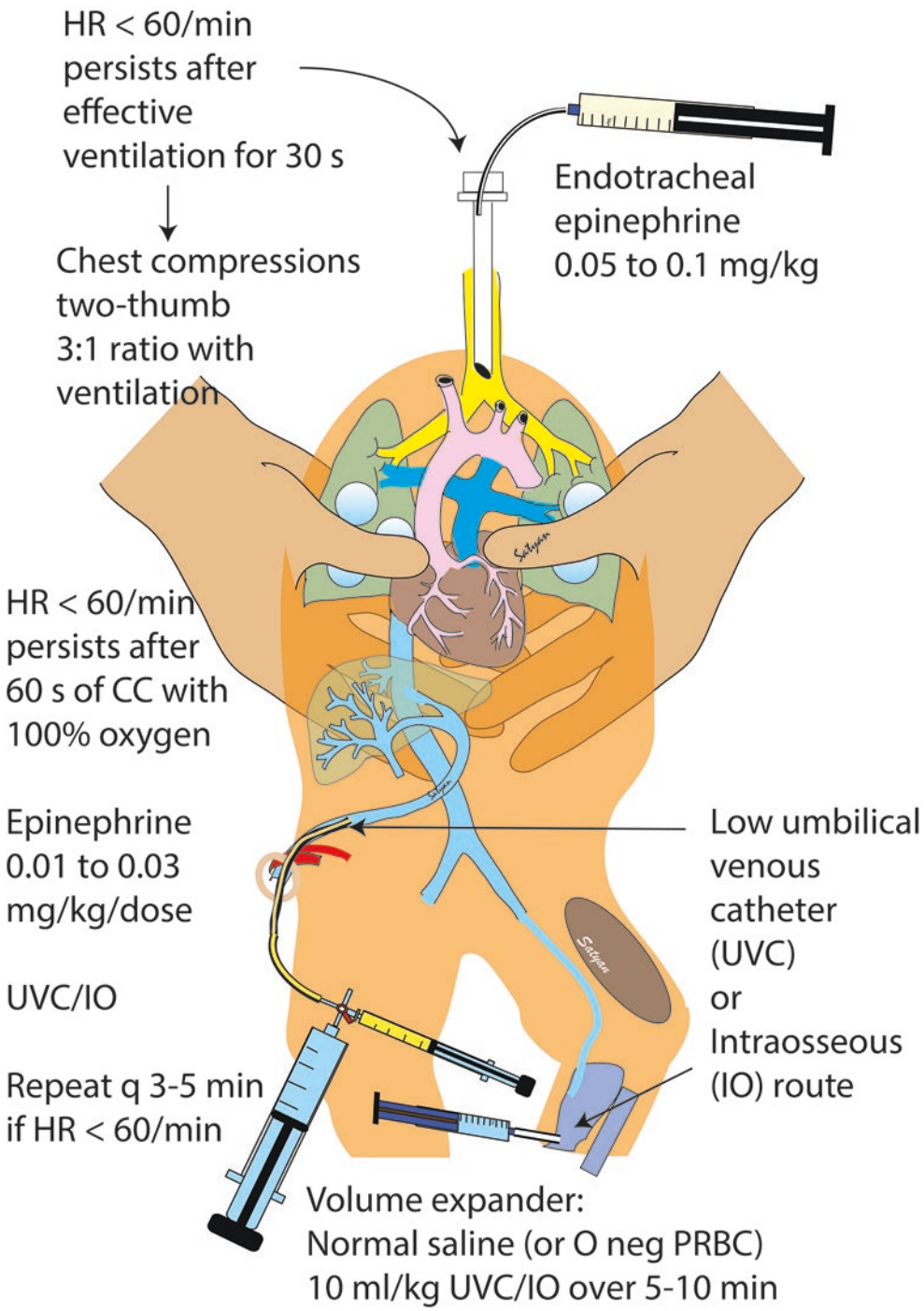


Fig. 19.20 Indications, dose, and routes of administration of epinephrine. *HR* heart rate, *UVC* umbilical venous catheter (low – 2 to 4 cm below skin surface), *IO* intraosseous. See text for details. Copyright Satyan Lakshminrusimha

Volume Expansion

Neonates who cannot be successfully resuscitated despite chest compression and epinephrine administration could be hypovolemic and may require a fluid bolus. Volume expansion should also be considered in the event of suspected blood loss (e.g., placental abruption, feto-maternal hemorrhage, twin anemia-polycythemia sequence). Normal saline and Ringer's lactate are appropriate choices for fluid resuscitation (Fig. 19.20). If blood loss is suspected, type O, Rh-negative blood administration is preferred when available. The use of albumin is discouraged owing to an observed association with increased mortality [53] and possible further exacerbation of transudation of fluid into the interstitial space in the asphyxiated acidotic state [54].

The recommended initial fluid bolus is 10 mL/kg and should be given no faster than over 5 min. Additional boluses may be given after clinical assessment and observation of

response. The neonatal heart is less compliant and has relative diastolic dysfunction. Administering an excess of fluids can have untoward hemodynamic effects. Furthermore, rapid infusion of volume can cause rapid changes in blood pressure, which can increase the risk of intraventricular hemorrhage in premature infants.

Discontinuation of Resuscitation

The decision to continue or discontinue resuscitative efforts should be individualized and should be considered at approximately 20 min after birth if no HR is observed after effective resuscitation.

Conclusion

Anesthesiologists often assist in critical aspects of neonatal resuscitation. Timely help in securing airway and assistance with respiratory and circulatory support are important in achieving good outcomes following resuscitation.

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Ethical and Medicolegal Considerations

20

Mariah K. Tanious and Thomas J. Mancuso

Ethical and medical-legal dilemmas frequently arise in the perioperative care of term and preterm neonates. This requires that pediatric anesthesiologists have a working knowledge of these ethical concerns in order to provide comprehensive care. Here we provide a concise review of common ethical challenges in the perioperative care of term and preterm neonates utilizing a widely accepted decision-making framework and then examine fundamental medical-legal concerns in neonatal care.

Reasoning About Ethical Concerns

The Four Principles Approach to Ethical Reasoning

In their landmark text *Principles of Biomedical Ethics*, bioethicists Tom Beauchamp and James Childress advocate that ethical dilemmas in clinical practice are most comprehensively considered by utilizing a framework structured upon four principles: autonomy, non-maleficence, beneficence, and justice [1]. That is, when confronting a difficult ethical dilemma in clinical practice, the four principles framework advocates that the clinician determines how to proceed by assessing the net balance of the salient concerns from the perspective of each principle. Notably for pediatric practitioners, the conceptual foundation of this framework rests on the perspective of the autonomous adult patient, and thus the four principles framework does not entirely transfer to all pediatric contexts. Nevertheless, the four principles framework is widely utilized by adult and pediatric bioethicists when resolving difficult ethical issues in the care of patients. Accordingly, it behooves the practicing pediatric anesthesiologist to be familiar with these concepts.

Limitations to the Four Principles Framework

Autonomy, from its Greek roots, literally means self-rule and is in many respects the foundation of the four principles framework. In ethics, autonomy commonly refers to an individual's freedom from control and their unconstrained ability to make profound life choices as they see fit. In the case of the neonate who has not developed the capacity to reason and make independent decisions about life choices, there can be no literal interpretation of this principle. Moreover, as mandated by legal regulations in nearly all US jurisdictions, and as supported by most pediatric ethicists, even loving parents are not free to autonomously make *any and all* medical decisions for their children, such as the refusal of blood component therapy in a life-threatening situation [2, 3]. Importantly, then, the foundational principal of autonomy or self-determination does not unequivocally reside even in parental decisions for their child. Parental autonomy is superseded, in part, by societal norms and standards to protect the minor as established by the Supreme Court of most countries.

Non-maleficence refers to the obligation of caregivers to avoid harm. In some clinical situations, agreement on what constitutes a harm would engender little debate, for example, failing to provide any perioperative analgesia to an infant suffering from significant pain after an invasive procedure would be considered a great harm by nearly all in our society. In other cases, such as a study requiring serial heel sticks in otherwise healthy neonates to study glucose trends, well-intended clinicians might reach opposite conclusions on whether such a research protocol represents, or does not represent, a harm [4]. The principle of *beneficence* is a continuum with non-maleficence but requires more of clinicians (and others) than not causing harm. The principle of

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beneficence requires clinicians to take active steps to ensure a positive benefit to the patient. Beneficence also includes the obligation to rescue persons from harm or harmful situations. This principle is interpreted from a translation of Hippocrates from his *Epidemics*: "As to disease, make a habit of two things, to help but at least do no harm." Yet, as with "harm," well-intentioned clinicians might not always agree on what constitutes a "benefit" in a particular clinical context. For example, some clinicians in a given context may strenuously advocate for continuing life-sustaining treatment because they conclude that the benefits outweigh the harms, whereas others may be equally certain, after assessing the same situation, that the harms of further treatment outweigh any potential benefit. The fourth principle, *justice*, refers to the provision of fair, equitable, and appropriate treatments to persons in light of what is owed to persons. As with the other principles, the concept of what constitutes justice is not free from differing interpretation by thoughtful clinicians or parents. Furthermore, the use of justice as an ethical principle is made more complex by the consideration of fairness and equality with respect to society, which may be especially challenging in cases involving scarce or financially burdensome resources. In sum, while the four principles approach to reasoning about ethical dilemmas provides a framework for clinicians to think comprehensively about all of the salient features, it cannot overcome variable interpretations of each of the principles that may prevent all parties to a given case from reaching similar conclusions on how to proceed.

Perioperative Applications of the Four Principles Framework

Autonomy

The biomedical principle of autonomy mandates informed consent to medical procedures for the adult with decision-making capacity. In the ideal process, the informed consent covers the risks and benefits of the proposed procedure, the risks and benefits of alternatives to the procedure, and the risks and benefits of doing nothing. In care of the neonate, parental permission necessarily replaces direct informed consent. True informed consent requires more than a signature on a closely typed form. The parents who give permission to caregivers must themselves understand the information, accept the care plan, and give voluntary permission without persuasion or manipulation.

The preanesthetic conversation, while often cursory, can and should be an opportunity for the pediatric anesthesiologist to inspire confidence and build rapport with the family as well as glean any important details about the infant before the procedure. Even for urgent or emergent cases, the parents have likely met and spent time with the surgeon. The pediatric anesthesiologist, however, often meets the family only immediately before the start of the procedure. This meeting may even take place in the holding area, not the ideal location or timing for an in-depth discussion of the risks, benefits, and options for anesthetic care.

The content of the informed permission conversation with the parents must be adapted to the context. In cases involving full-term neonates scheduled for relatively elective or urgent procedures such as pyloromyotomy, circumcision, or herniorrhaphy, it very well may be that the risk, small as it may be, from the provision of anesthesia is significantly greater that that posed by the surgical procedure itself. The parents may express their concern to the pediatric anesthesiologist in these situations with statements such as: "My baby is not likely to suffer from his hernia repair, but I am very worried about the anesthesia." Discussion of the possible deleterious effects of various anesthetic medications on the developing central nervous system is an important and frequently cited parental concern, which is reviewed in more detail beyond this chapter. In addition to a review of this issue and other relevant anesthetic concerns, the pediatric anesthesiologist should engage in a frank and understandable exchange with the parents, asking open-ended questions and providing them with time and space to weigh all of their concerns regarding the anesthetic.

Many surgical cases involving neonates are much more significant and emergent in nature, however. In these cases, often involving preterm neonates, the risks from the condition afflicting the neonate and from the surgery itself may be quite significant, reducing the anesthetic care to a resuscitation more than the provision of analgesia, unconsciousness, and vital sign stability. The question of cardiopulmonary resuscitation (CPR) may even be part of the preanesthetic discussion. In such cases, the pediatric anesthesiologist should have a discussion with both the surgeon and neonatologist in order to appreciate the gravity of the neonate's condition and what can be expected in the operating room. It may be appropriate to have a preanesthetic discussion with the parents, surgeon, and the neonatal intensive care unit physicians and nurses in order to minimize the chances in this very stressful situation that the family becomes confused and unduly anxious as a result of hearing similar information, but with different emphasis and language from different sources. In consideration of difficult cases like these, Pinter has proposed classifying surgical neonates according to their chances for recovery and the quality of life should the neonate recover [5]. The details of the classification are not as important as ensuring that the parents understand, as much as possible, the immediate as well as longer-term prognosis, all before signing the consent. Other authors, such as Caniano, reviewed neonatal surgery and highlighted the important differences between simply survival and a benefit to the neonate [6],

whereas Lorenz reviewed the important ethical considerations in the management of preterm neonates at the extremes of viability and indicated the primacy of the neonate's best interest in these difficult choices [7]. Parents are considered by all of these commentators to be the persons best suited to determine and advocate for the best interests of their neonate, once again underscoring the importance of the preanesthetic discussions.

Non-maleficence

The principle of non-maleficence comes into importance especially in the care of neonates at the extremes of viability and/or with such serious surgical conditions that survival is in doubt and prognosis grim. Harm, as defined by Beauchamp and Childress, means an unjustifiable setback or defeat of a person's interests [1]. They also limit their definition to physical harms. As mentioned, parents are generally, but not unequivocally, considered the prima facie authority to determine the best interests for the neonate. Yet, some have argued that the best interest standard is insufficient for severely impaired infants and instead advocate for additional viewpoints in the evaluation of care provided to these unfortunate neonates [8]. Proponents of this view argue that the suffering of infants is not given sufficient weight and propose that severely impaired infants have the right to a dignified death and support palliative as opposed to intensive care for these unfortunate patients.

The Committee of the Fetus and Newborn (COFN) of the American Academy of Pediatrics (AAP) addressed the issue of determining an infant's best interests. In a policy statement on high-risk neonates, the Committee notes, "…intensive treatment of all severely ill infants may result in the prolongation of dying accompanied by significant discomfort for the infant or survival with unacceptable quality of life…non-intensive treatment may result in increased mortality and morbidity….either approach risks undesired and unpredictable results" [9]. The COFN also notes the importance of the parents' role in decision-making regarding the care of these critically ill neonates but also reemphasizes that the physician's first responsibility is to the patient. The Committee further states that physicians are not required to provide treatment that they consider to be inappropriate or to withhold beneficial treatments [10]. In cases of honest disagreement, the COFN recommends that the hospital bioethics committee become involved to resolve the issues. In practice, there may be insufficient time for this to occur, and the pediatric anesthesiologist must personally decide if their personal morals allow them to participate in the care of a particular neonate. Last, the Committee's policy statement notes the following:

- In cases where there is little or no chance for survival, CPR should not be begun.
- In cases where survival is possible but a good outcome is unlikely, the (well-informed) parental preferences should guide whether or not CPR be instituted.
- In cases where a good outcome is considered more likely, CPR should be undertaken and continual reevaluation of the utility of continued intensive care be undertaken [10].

Beneficence

There are two aspects of beneficence: Positive beneficence requires that clinicians act to increase the welfare of patients, while utility requires clinicians to balance the benefits and burdens of an action and choose the action leading to the best overall result [1]. The utility aspect of beneficence becomes relevant to pediatric anesthesiologists in terms of assessment of the risks and benefits of appropriate anesthetic care for an operation or procedure and in the management of pain in the neonate in both intraoperative and postoperative periods [11]. The principle of utility serves as a useful decision-making framework in these situations since anesthetic agents have immediate deleterious cardiovascular effects as well as possibly longer-term effects on the developing central nervous system of the neonate. In the postoperative period, assessing the adequacy of analgesia can also be quite problematic. There are a variety of pain assessment tools available for the neonate for evaluation of acute, procedural, and chronic pain [12]. These tools include both physiologic and behavioral components and will be most effective only if all caregivers have ongoing training in their use. Yet even in the case of clearly suboptimal pain control, analgesics present both benefits and potential harms to the neonate. Careless use of analgesics in any neonate can lead to significant cardiopulmonary derangements. A proper balance of the benefits and harms of such essential treatment as adequate pain relief begins with clinically competent assessment of the patient and appropriate dosing of any medication.

In sum, ethical considerations of benefit and harm are inextricably linked to competent clinical care. This is particularly relevant to the provision of palliative care to infants with a life-threatening and/or terminal condition in which the unique training and expertise of the pediatric anesthesiologist can guide the development and implementation of effective treatment regimens with minimal untoward effects [13].

Justice

The concept of what constitutes justice in the context of healthcare is more problematic as there are widely differing views in our plural society. Barnum describes what she calls "benevolent injustice," an outcome in which an infant survives a difficult neonatal course but with significant morbidity such that they depend on significant technological support. She quotes Norman Daniel's definition of justice as it applies to healthcare as the maintenance of normal function

and then describes it as an injustice when healthcare fails in its primary function to maintain normal functioning of the individual neonate. Barnum elaborates that a benevolent injustice occurs when well-intentioned treatment leaves a neonate with significant morbidity and disabilities [14]. Recently, outcomes of perinatal care in the United States were compared with that in several other countries, including Australia, Canada, and the United Kingdom. Care in the United States differed from these other countries in providing proportionally less prenatal care but having proportionally more intensive care nursery capacity and expended significantly more resources on neonatal intensive care. Low birth weights were seen more often in the United States though the relative risk for overall neonatal mortality did not differ significantly among the four countries [15].

Case Example: In the case of the neonate born to a family of the Jehovah's Witnesses faith, the Supreme Court in both the United States and Canada have ruled that blood products cannot be withheld if the neonate's life is believed to be in jeopardy. The tacit assumption is that the child would follow the parent's religion and hence would refuse blood even in the face of death. However, the Supreme Court have ruled that this assumption may not hold true and until the neonate reaches the age of maturity to make such a decision, society must protect the child and provide the lifesaving treatment.

It has been the editors' experience through encounters with the Medical Liaison Committee of the Jehovah's Witnesses that when a face-to-face discussion takes place between the members of the Committee, the parents and the medical team, and the care team describes all efforts will be made to optimize the neonate before surgery, to implement all blood-saving measures and to minimize all blood loss during surgery, it becomes unnecessary to proceed to court to make the neonate a ward of the state for the period of the surgery. It has likewise been the editors' experience that following such discussions, although the parents may remain steadfast and refuse to consent to a blood transfusion for their neonate, they do understand and respect the efforts expended by the medical team to respect their beliefs and, in most circumstances, will consent to the anesthesia and surgery.

Perioperative Do-Not-Resuscitate Orders

Neonates with existing do-not-resuscitate (DNR) orders may require anesthesia for palliation or for placement of devices that simplify care such as a gastrostomy tube, tracheostomy, or central line. Underlying the decision to invoke a DNR order is typically the premise that the neonate has a terminal or irreversible condition and that a cardiac arrest, if it were to occur, will leave the patient in yet a worse condition, even if the resuscitation were successful. DNR orders are most often established when the parents have already decided to limit care or when a cardiac or respiratory arrest has previously occurred; these orders precede death by a matter of days on average [16]. Accordingly, resuscitation in this context is not warranted. Yet, this premise does not hold in the perioperative setting because anesthetic medications inherently induce some degree of cardiorespiratory instability, which anesthesiologists expect and are present to ameliorate, if not reverse.

The American Society of Anesthesiologists (ASA) has promulgated recommendations for the care of patients with a DNR order who undergo anesthesia [17]. These recommendations strongly disagree with routine suspension of the DNR order for patients undergoing anesthesia for procedures and instead endorse a discussion among the caregivers and family members before the procedure on the overall goals of care and the extent to which resuscitation measures will be applied.

More recently, the American Academy of Pediatrics has also put forth a statement advocating a similar approach [18]. This report describes three approaches to DNR orders for children who come to the OR for anesthesia and surgery: full resuscitation, a goal-directed approach, or a procedure-directed approach. The informed consent process assumes particular importance in these cases as it is likely that neither the surgeon nor the anesthesiologist was involved in the decision to invoke the DNR order. During the preanesthetic visit, the presence of the child's primary neonatal physician as well as the surgeon would ensure that all members of the medical team participate in a discussion with the family to reach a congruous approach to the DNR order in the operating room.

With the procedure-directed approach to anesthetic care of these neonates, the details of intraoperative care must be carefully reviewed with the family. If the trachea is not intubated, but the procedure would generally be done with an anesthetic technique that would include tracheal intubation, this must be discussed in detail with the family. In addition, other possible eventualities that would be routinely managed in the provision of an anesthetic and that would otherwise be considered resuscitation such as stabilizing abnormal vital signs and rapid administration of intravenous fluids, blood, or blood products must be reviewed.

Others have advocated for a goal-directed approach to the anesthetic care of children with a DNR order in place [19]. In this approach, the medical details of perioperative care are less important than understanding and respecting the goal of the family vis-à-vis the procedure. This approach does not specify the details of anesthetic care as they are specified in the procedure-directed approach. Rather, the concept here is to utilize any techniques that are consistent with the overall goal of care that is established in the preanesthetic meeting

with the family. An additional concept of great importance in this context is that whenever a DNR order is transiently altered in order to perform a procedure, whether suspended, or a procedure-directed or goal-directed approach is adopted, it is essential to clearly define a priori when these changes will commence and when they will cease. Advanced agreement among the parents and caregivers on the timing for resumption of the DNR order must be respected unless all parties agree that circumstances warrant revision of the preanesthetic treatment plan. Failure to do so is a certain recipe for ethical conflict.

In addition to specific approaches to discuss perioperative DNR orders, pediatric anesthesiologists, along with neonatologists and pediatric surgeons, benefit from use of a shared decision-making (SDM) model [20, 21]. This methodology has been widely published and is a helpful model for the perioperative care of critically ill neonates. There are challenges to its use, however, in situations when the parental values and the neonate prognosis are uncertain. These choices are often made in very emotionally stressful moments further complicated by, in many cases, the pressures of time [22]. Leaders in the field describe utilization of the "best interests of the child" standard or the more comprehensive biopsychosocial framework to guide discussions with parents and to weigh benefits/risks of different interventions [23].

Regulatory Concerns in Perinatal Care

The Baby Doe Regulation Controversy

Few regulations have generated as much confusion and controversy as the so-called "Baby Doe" regulations [24]. Baby Doe was an infant with Down syndrome and tracheoesophageal fistula born in Bloomington, Indiana, in 1982. His parents declined corrective surgery on the grounds that he would never achieve a "minimally acceptable quality of life," and the child subsequently died. The case generated public controversy. After a number of appeals, the final Baby Doe regulations, often referred to as the "Final Rule," were passed by the Congress as the 1984 Amendments to the Child Abuse Prevention and Treatment Act [25]. This legislation required all states to create a regulatory system to investigate cases where medically indicated treatment is withheld from handicapped infants or states would risk the withholding of federal funding for children's services. It also stipulated that "the withholding of medically indicated treatment from a disabled infant with a life-threatening condition" by parents or providers was considered medical neglect. The legislation then outlined three medical conditions that would justify withholding otherwise required treatment. According to the Final Rule legislation: "The term 'withholding of medically indicated treatment' means the failure to respond to the infant's life threatening conditions by providing treatment (including appropriate nutrition, hydration, and medication) which, in the treating physician's reasonable medical judgment, will be most likely to be effective in ameliorating or correcting all such conditions, except that the term does not include the failure to provide treatment (other than appropriate nutrition, hydration, or medication) to an infant when, in the treating physician's reasonable medical judgment any of the following circumstances apply:

(i) The infant is chronically and irreversibly comatose;
(ii) The provision of such treatment would merely prolong dying, and not be effective in ameliorating or correcting the infant's life-threatening conditions, or otherwise be futile in terms of survival of the infant; or.
(iii) The provision of such treatment would be virtually futile in terms of survival of the infant and the treatment itself under such circumstances would be inhumane." [26].

Many argue that the Baby Doe regulations are not helpful in decision-making for infants because of ambiguity regarding the term "appropriate." Regardless of how one interprets the intentions of the Final Rule legislation, this is not a commonly recommended framework for ethical decision-making at the end-of-life in the child. The American Academy of Pediatrics (AAP) Committee on Fetus and Newborn (COFN) describes the foundations upon which difficult decisions about resuscitation rest: clear, open communication between the healthcare team and the family, active involvement of the family in decision-making, continued care when ICU care is stopped, and finally, that treatment be guided by the best interests of the child [9]. In a more recent clinical report, COFN again emphasized the importance of individualized consideration of all factors by the care team and the parents before reaching a decision about resuscitation [10]. Other commentators have noted that the literal interpretation of the regulation mandates the treatment of all critically ill neonates under all circumstances, and even possibly against the wishes of loving and informed parents, and the professional opinion of the clinicians, leading to permanent care of all infants, no matter how devastated and compromised. Few would agree that such an inflexible approach to every infant's care is wise [27].

Born Alive Infant Protection Act

Subsequent to the Baby Doe regulations, the Born Alive Infant Protection Act (BAIPA) was passed in 2002. This law

extends the definitions of "person" or "child" to include "every infant member of homo sapiens who is born alive at any stage of development" [28]. Sayeed quotes from the deliberations that the law was enacted "to repudiate the flawed notion that a child's entitlement to the protections of the law is dependent on whether that child's' mother or others want him or her" [29, 30]. Later, in 2005, the Department of Health and Human Services announced that enforcement of regulations was affected by that law (BAIPA) with mention of the Emergency Medical Treatment and Active Labor Act (EMTALA). The EMTALA statute requires medical practitioners and institutions to provide care to individuals with an emergency condition regardless of that individual's ability to pay. Taken together, these two acts could restrict or eliminate any practitioner or parental discretion regarding resuscitation of very low gestational age neonates. There is much confusion about the exact meaning of the regulations, and various interpretations of the regulations have been published. The AAP COFN, in their policy statement Noninitiation or Withdrawal of Intensive Care for High Risk Newborns, does not mention these regulations [9]. The AAP Neonatal Resuscitation Steering Committee commented in a letter to the editor in *Pediatrics* that BAIPA "should not, in any way affect the approach that physicians currently follow with respect to extremely premature infants." [31] The AAP Committee on Bioethics, in their statement Ethics and the Care of Critically Ill Children, opined that physicians may have more discretion in redirecting care of critically ill neonates than is commonly realized, citing exceptions to the mandate to provide treatment except in cases where it is "futile" or "virtually futile" [10]. Other authors have similarly noted the unique "zone of parental discretion" that exists in the case of neonates at the extremes of viability, where a parental decision to either palliate or to aggressively resuscitate is equally ethically defensible [32]. The AAP further supports the importance of parental involvement in these difficult life and death decisions along with the reasoned medical judgments of the newborn medicine physicians [9, 10].

Conclusions

Superb anesthetic care of neonates requires an extensive knowledge of the unique physiology of these, our smallest and most vulnerable patients. Yet, this alone is insufficient to the provision of comprehensive care of the neonate. The pediatric anesthesiologist must equally have a working knowledge of the ethical and regulatory concerns peculiar to the neonate. In nearly all instances, clear and open communication with the parents and the neonatal medical team will identify issues of ethical concern and pave the way to determining the optimal prescription for each neonate.

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